CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 9/00

A2

(11) International Publication Number: WO 99/53036

(43) International Publication Date: 21 October 1999 (21.10.99)

(21) International Application Number: PCT/US99/08150

(22) International Filing Date: 13 April 1999 (13.04.99)

(30) Priority Data:
60/081,784 14 April 1998 (14.04.98) US

(71) Applicant (*for all designated States except US*): SUGEN, INC. [US/US]; 230 East Grand Avenue, South San Francisco, CA 94080 (US).

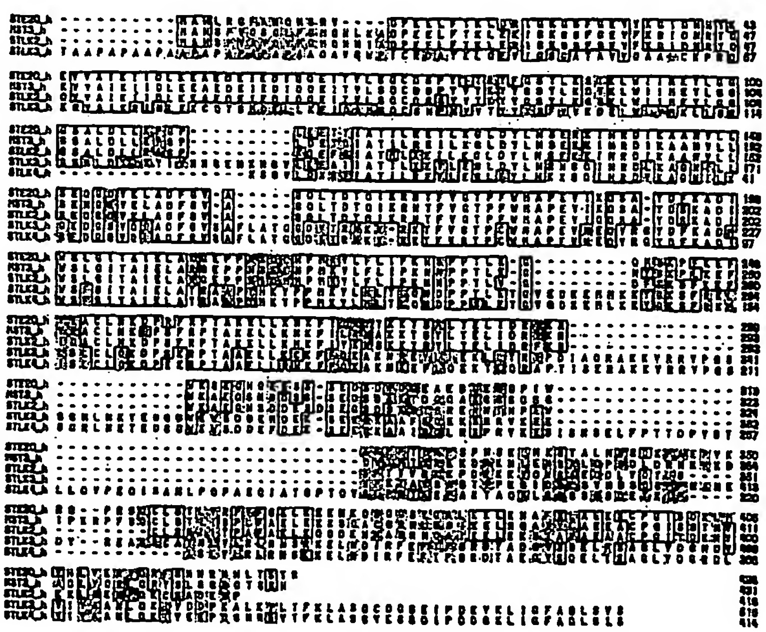
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): PLOWMAN, Gregory [US/US]; 4 Honeysuckle Lane, San Carlos, CA 94070 (US). MARTINEZ, Ricardo [US/US]; 984 Cartier Lane, Foster City, CA 94404 (US). WHYTE, David [US/US]; 2623 Barclay Way, Belmont, CA 94002 (US).

(74) Agents: WARBURG, Richard, J. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: STE20-RELATED PROTEIN KINASES



(57) Abstract

The present invention relates to the novel kinase polypeptides STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, nucleotide sequences encoding the novel kinase polypeptides, as well as various products and methods useful for the diagnosis and treatment of various kinase-related diseases and conditions.

*(Referred to in PCT Gazette No. 7/2000, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

DESCRIPTION

STE20-RELATED PROTEIN KINASES

RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Patent Application Serial No. 60/081,784 by Plowman and Martinez, entitled STE20-Related Protein kinases, filed April 14, 1998 (Lyon & Lyon Docket No. 232/279), hereby incorporated by reference herein in its entirety, including any drawings, tables, or figures.

FIELD OF THE INVENTION

The present invention relates to novel kinase polypeptides, nucleotide sequences encoding the novel kinase polypeptides, as well as various products and methods useful for the diagnosis and treatment of various kinase-related diseases and conditions.

BACKGROUND OF THE INVENTION

The following description of the background of the invention is provided to aid in understanding the invention, but is not admitted to be or to describe prior art to the invention.

Cellular signal transduction is a fundamental mechanism whereby external stimuli that regulate diverse cellular processes are relayed to the interior of cells. One of the key biochemical mechanisms of signal transduction involves the reversible phosphorylation of proteins, which enables regulation of the activity of mature proteins by altering their structure and function.

The best characterized protein kinases in eukaryotes phosphorylate proteins on the hydroxyl moiety of serine, threonine and tyrosine residues. These kinases largely fall

into two groups, those specific for phosphorylating serines and threonines, and those specific for phosphorylating tyrosines. Some kinases, referred to as "dual specificity" kinases, are able to phosphorylate on tyrosine as well as serine/threonine residues.

Protein kinases can also be characterized by their location within the cell. Some kinases are transmembrane receptor-type proteins capable of directly altering their catalytic activity in response to the external environment such as the binding of a ligand. Others are non-receptor-type proteins lacking any transmembrane domain. They can be found in a variety of cellular compartments from the inner surface of the cell membrane to the nucleus.

Many kinases are involved in regulatory cascades wherein their substrates may include other kinases whose activities are regulated by their phosphorylation state. Ultimately the activity of some downstream effector is modulated by phosphorylation resulting from activation of such a pathway.

Protein kinases are one of the largest families of eukaryotic proteins with several hundred known members. These proteins share a 250-300 amino acid domain that can be subdivided into 12 distinct subdomains that comprise the common catalytic core structure. These conserved protein motifs have recently been exploited using PCR-based cloning strategies leading to a significant expansion of the known kinases.

Multiple alignment of the sequences in the catalytic domain of protein kinases and subsequent parsimony analysis permits the segregation of related kinases into distinct branches or subfamilies including: tyrosine kinases, cyclic-nucleotide-dependent kinases, calcium/calmodulin kinases, cyclin-dependent kinases and MAP-kinases, serine-

threonine kinase receptors, and several other less defined subfamilies.

SUMMARY OF THE INVENTION

Through the use of a targeted PCR cloning strategy and of a "motif extraction" bioinformatics script, mammalian members of the STE20-kinase family have been identified as part of the present invention. Multiple alignment and parsimony analysis of the catalytic domain of all of these STE20-family members reveals that these proteins cluster into 9 distinct subgroups. Classification in this manner has proven highly accurate not only in predicting motifs present in the remaining non-catalytic portion of each protein, but also in their regulation, substrates, and signaling pathways. The present invention includes the partial or complete sequence of new members of the STE20-family, their classification, predicted or deduced protein structure, and a strategy for elucidating their biologic and therapeutic relevance.

Thus, a first aspect of the invention features an isolated, enriched, or purified nucleic acid molecule encoding a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

By "isolated" in reference to nucleic acid is meant a polymer of nucleotides conjugated to each other, including DNA and RNA, that is isolated from a natural source or that is synthesized. The isolated nucleic acid of the present invention is unique in the sense that it is not found in a pure or separated state in nature. Use of the term "isolated" indicates that a naturally occurring sequence has been removed from its normal cellular (*i.e.*, chromosomal) environment. Thus, the sequence may be in a cell-free

solution or placed in a different cellular environment. The term does not imply that the sequence is the only nucleotide chain present, but that it is essentially free (about 90 - 95% pure at least) of non-nucleotide material naturally associated with it, and thus is distinguished from isolated chromosomes.

By the use of the term "enriched" in reference to nucleic acid is meant that the specific DNA or RNA sequence constitutes a significantly higher fraction (2 - 5 fold) of the total DNA or RNA present in the cells or solution of interest than in normal or diseased cells or in the cells from which the sequence was taken. This could be caused by a person by preferential reduction in the amount of other DNA or RNA present, or by a preferential increase in the amount of the specific DNA or RNA sequence, or by a combination of the two. However, it should be noted that enriched does not imply that there are no other DNA or RNA sequences present, just that the relative amount of the sequence of interest has been significantly increased. The term "significant" is used to indicate that the level of increase is useful to the person making such an increase, and generally means an increase relative to other nucleic acids of about at least 2 fold, more preferably at least 5 to 10 fold or even more. The term also does not imply that there is no DNA or RNA from other sources. The other source DNA may, for example, comprise DNA from a yeast or bacterial genome, or a cloning vector such as pUC19. This term distinguishes from naturally occurring events, such as viral infection, or tumor type growths, in which the level of one mRNA may be naturally increased relative to other species of mRNA. That is, the term is meant to cover only those situations in which a person has intervened to elevate the proportion of the desired nucleic acid.

It is also advantageous for some purposes that a nucleotide sequence be in purified form. The term "purified" in reference to nucleic acid does not require absolute purity (such as a homogeneous preparation). Instead, it represents an indication that the sequence is relatively more pure than in the natural environment (compared to the natural level this level should be at least 2-5 fold greater, *e.g.*, in terms of mg/mL). Individual clones isolated from a cDNA library may be purified to electrophoretic homogeneity. The claimed DNA molecules obtained from these clones could be obtained directly from total DNA or from total RNA. The cDNA clones are not naturally occurring, but rather are preferably obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The construction of a cDNA library from mRNA involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection of the cells carrying the cDNA library. Thus, the process which includes the construction of a cDNA library from mRNA and isolation of distinct cDNA clones yields an approximately 10^6-fold purification of the native message. Thus, purification of at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

By a "kinase polypeptide" is meant 32 (preferably 40, more preferably 45, most preferably 55) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or the corresponding full-length amino acid sequence; 250 (preferably 255, more preferably 260, most preferably 270) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:105, or the

corresponding full-length amino acid sequence; 27 (preferably 30, more preferably 40, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:18; 16 (preferably 20, more preferably 25, most preferably 35) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, or SEQ ID NO:103 or the corresponding full-length amino acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101, or the corresponding full-length amino acid sequence; 78 (preferably 80, more preferably 85, most preferably 90) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:107 or functional derivatives thereof as described herein. For sequences for which the full-length sequence is not given, the remaining sequences can be determined using methods well-known to those in the art and are intended to be included in the invention. In certain aspects, polypeptides of 100, 200, 300 or more amino acids are preferred. The kinase polypeptide can be encoded by a full-length nucleic acid sequence or any portion of the full-length nucleic acid sequence, so long as a functional activity of the polypeptide is retained, not to include fragments containing only amino acids 1-22 of SEQ ID NO:13 or only amino acids 1-33 of SEQ ID NO:107.

The amino acid sequence will be substantially similar to the sequence shown in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID

NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, or fragments thereof, not to include fragments consisting only of the amino acid sequences 1-22 of SEQ ID NO:13 or 1-33 of SEQ ID NO:107. A sequence that is substantially similar to the sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107 will preferably have at least 90% identity (more preferably at least 95% and most preferably 99-100%) to the sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107.

By "identity" is meant a property of sequences that measures their similarity or relationship. Identity is measured by dividing the number of identical residues by the total number of residues and gaps and multiplying the product by 100. "Gaps" are spaces in an alignment that are the result of additons or deletions of amino acids. Thus, two copies of exactly the same sequence have 100% identity, but sequences that are less highly conserved, and have deletions, additions, or replacements, may have a lower degree of identity. Those skilled in the art will recognize that several computer programs are available for determining sequence identity using standard parameters, for example Blast (Altschul, *et al.* (1997) Nucleic Acids Res. 25:3389-3402), Blast2 (Altschul, *et al.* (1990) J. mol. biol. 215:403-410), and Smith-Waterman (Smith, *et al.* (1981) J. Mol. Biol. 147:195-197).

In preferred embodiments, the invention features isolated, enriched, or purified nucleic acid molecules encoding a kinase polypeptide comprising a nucleotide sequence that: (a) encodes a polypeptide having the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107; (b) is the complement of the nucleotide sequence of (a); (c) hybridizes under highly stringent conditions to the nucleotide molecule of (a) and encodes a naturally occurring kinase polypeptide; (d) encodes a kinase polypeptide having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO: 103, SEQ ID NO:105, or SEQ ID NO:107, except that it lacks one or more, but not all, of the following segments of amino acid residues: 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489 or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 1-22, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 284-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID NO:99, 1-52, 53-173, 174-

307, 308-572, or 573-591 of SEQ ID NO:103, 1-24, 25-289, 290-397, 398-628, 629-872, or 873-1227 of SEQ ID NO:105, or 1-33, 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107; (e) is the complement of the nucleotide sequence of (d); (f) encodes a polypeptide having the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31; SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107 from amino acid residues 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489, or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 282-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID NO:103, 1-24, 25-289, 290-397, 398-628, 629-872, or 873-1227 of SEQ ID NO:105,or 1-33, 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107; (g) is the complement of the nucleotide sequence of (f);(h) encodes a polypeptide having the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID

NO:105, or SEQ ID NO:107, except that it lacks one or more of the domains selected from the group consisting of a N-terminal domain, a catalytic domain, a C-terminal domain, a coiled-coil structure region, a proline-rich region, a spacer region, an insert, and a C-terminal tail; or (i) is the complement of the nucleotide sequence of (h).

The term "complement" refers to two nucleotides that can form multiple favorable interactions with one another. For example, adenine is complementary to thymine as they can form two hydrogen bonds. Similarly, guanine and cytosine are complementary since they can form three hydrogen bonds. A nucleotide sequence is the complement of another nucleotide sequence if all of the nucleotides of the first sequence are complementary to all of the nucleotides of the second sequence.

The term "domain" refers to a region of a polypeptide which contains a particular function. For instance, N-terminal or C-terminal domains of signal transduction proteins can serve functions including, but not limited to, binding molecules that localize the signal transduction molecule to different regions of the cell or binding other signaling molecules directly responsible for propagating a particular cellular signal. Some domains can be expressed separately from the rest of the protein and function by themselves, while others must remain part of the intact protein to retain function. The latter are termed functional regions of proteins and also relate to domains.

The term "N-terminal domain" refers to the extracatalytic region located between the initiator methionine and the catalytic domain of the protein kinase. The N-terminal domain can be identified following a Smith-Waterman alignment of the protein sequence against the non-redundant protein database to define the N-terminal boundary

of the catalytic domain. Depending on its length, the N-terminal domain may or may not play a regulatory role in kinase function. An example of a protein kinase whose N-terminal domain has been shown to play a regulatory role is PAK65, which contains a CRIB motif used for Cdc42 and rac binding (Burbelo, P.D. et al. (1995) J. Biol. Chem. 270, 29071-290740).

The N-terminal domain spans amino acid residues 1-21 of the sequence set forth in SEQ ID NO:5, amino acid residues 1-31 of the sequence set forth in SEQ ID NO:6, amino acid residues 1-22 of the sequence set forth in SEQ ID NO:13, amino acid residues 1-13 of the sequence set forth in SEQ ID NO:18, amino acid residues 1-21 of the sequence set forth in SEQ ID NO:22, amino acid residues 1-25 of the sequence set forth in SEQ ID NO:24, amino acid residues 1-51 of the sequence set forth in SEQ ID NO:29, amino acid residues 1-25 of the sequence set forth in SEQ ID NO:31, amino acid residues 1-57 of the sequence set forth in SEQ ID NO:99, amino acid residues 1-52 of the sequence set forth in SEQ ID NO:103, amino acid residues 1-24 of the sequence set forth in SEQ ID NO:105, or amino acid residues 1-33 of the sequence set forth in SEQ ID NO:107.

The term "catalytic domain" refers to a region of the protein kinase that is typically 25-300 amino acids long and is responsible for carrying out the phosphate transfer reaction from a high-energy phosphate donor molecule such as ATP or GTP to itself (autophosphorylation) or to other proteins (exogenous phosphorylation). The catalytic domain of protein kinases is made up of 12 subdomains that contain highly conserved amino acid residues, and are responsible for proper polypeptide folding and for catalysis. The catalytic domain can be identified following a Smith-

Waterman alignment of the protein sequence against the non-redundant protein database.

The catalytic domain spans amino acid residues 22-274 of the sequence set forth in SEQ ID NO:5, residues 32-308 of the sequence set forth in SEQ ID NO:6, residues 1-178 of the sequence set forth in SEQ ID NO:7, residues 23-289 of the sequence set forth in SEQ ID NO:13, residues 1-255 of the sequence set forth in SEQ ID NO:14, residues 1-255 of the sequence set forth in SEQ ID NO:15, residues 14-273 of the sequence set forth in SEQ ID NO:18, residues 22-277 of the sequence set forth in SEQ ID NO:22, residues 1-66 of the sequence set forth in SEQ ID NO:23, residues 26-273 of the sequence set forth in SEQ ID NO:24, residues 394-658 of the sequence set forth in SEQ ID NO:29, residues 26-281 of the sequence set forth in SEQ ID NO:31, residues 1-278 of the sequence set forth in SEQ ID NO:97, residues 58-369 of the sequence set forth in SEQ ID NO:99, residues 1-103 of the sequence set forth in SEQ ID NO:101, residues 308-572 of the sequence set forth in SEQ ID NO:103, residues 25-289 of the sequence set forth in SEQ ID NO:105, or residues 34-294 of the sequence set forth in SEQ ID NO:107.

The term "catalytic activity", as used herein, defines the rate at which a kinase catalytic domain phosphorylates a substrate. Catalytic activity can be measured, for example, by determining the amount of a substrate converted to a phosphorylated product as a function of time. Catalytic activity can be measured by methods of the invention by holding time constant and determining the concentration of a phosphorylated substrate after a fixed period of time. Phosphorylation of a substrate occurs at the active-site of a protein kinase. The active-site is normally a cavity in which the substrate binds to the protein kinase and is phosphorylated.

The term "substrate" as used herein refers to a molecule phosphorylated by a kinase of the invention. Kinases phosphorylate substrates on serine/threonine or tyrosine amino acids. The molecule may be another protein or a polypeptide.

The term "C-terminal domain" refers to the region located between the catalytic domain or the last (located closest to the C-terminus) functional domain and the carboxy-terminal amino acid residue of the protein kinase. By "functional" domain is meant any region of the polypeptide that may play a regulatory or catalytic role as predicted from amino acid sequence homology to other proteins or by the presence of amino acid sequences that may give rise to specific structural conformations (*i.e.* coiled-coils). The C-terminal domain can be identified by using a Smith-Waterman alignment of the protein sequence against the non-redundant protein database to define the C-terminal boundary of the catalytic domain or of any functional C-terminal extracatalytic domain. Depending on its length and amino acid composition, the C-terminal domain may or may not play a regulatory role in kinase function. An example of a protein kinase whose C-terminal domain may play a regulatory role is PAK3 which contains a heterotrimeric G_b subunit-binding site near its C-terminus (Leeuw, T. et al (1998) Nature, 391, 191-195).

The C-terminal domain spans amino acid residues 275-416 of the sequence set forth in SEQ ID NO:5, residues 309-489 of the sequence set forth in SEQ ID NO:6, residues 179-414 of the sequence set forth in SEQ ID NO:7, residues 897-1239 of the sequence set forth in SEQ ID NO:13, residues 955-1297 of the sequence set forth in SEQ ID NO:14, residues 984-1326 of the sequence set forth in SEQ ID NO:15, residues 535-894 of the sequence set forth in SEQ ID NO:18, residues 752-898

of the sequence set forth in SEQ ID NO:22, residues 279-330 of the sequence set forth in SEQ ID NO:97, residues 370-418 of the sequence set forth in SEQ ID NO:99, or residues 873-1227 of the sequence set forth in SEQ ID NO:105.

The term "signal transduction pathway" refers to the molecules that propagate an extracellular signal through the cell membrane to become an intracellular signal. This signal can then stimulate a cellular response. The polypeptide molecules involved in signal transduction processes are typically receptor and non-receptor protein tyrosine kinases, receptor and non-receptor protein phosphatases, SRC homology 2 and 3 domains, phosphotyrosine binding proteins (SRC homology 2 (SH2) and phosphotyrosine binding (PTB and PH) domain containing proteins), proline-rich binding proteins (SH3 domain containing proteins), nucleotide exchange factors, and transcription factors.

The term "coiled-coil structure region" as used herein, refers to a polypeptide sequence that has a high probability of adopting a coiled-coil structure as predicted by computer algorithms such as COILS (Lupas, A. (1996) Meth. Enzymology 266:513-525). Coiled-coils are formed by two or three amphipathic α-helices in parallel. Coiled-coils can bind to coiled-coil domains of other polypeptides resulting in homo- or heterodimers (Lupas, A. (1991) Science 252:1162-1164). Coiled-coil-dependent oligomerization has been shown to be necessary for protein function including catalytic activity of serine/threonine kinases (Roe, J. *et al.* (1997) J. Biol. Chem. 272:5838-5845).

The coiled-coil structure region spans amino acid residues 290-526 of the sequence set forth in SEQ ID NO:13, residues 256-442 of the sequence set forth in SEQ ID NO:14, residues 256-476 of the sequence set forth in SEQ ID NO:15, residues 428-637 of the sequence set forth in SEQ ID NO:22,

residues 216-425 or 540-786 of the sequence set forth in SEQ ID NO:23, residues 423-632 of the sequence set forth in SEQ ID NO:24, residues 431-640 or 755-901 of the sequence set forth in SEQ ID NO:31, residues 291-398 or 629-668 of the sequence set forth in SEQ ID NO:105, or residues 473-724 or 725-968 of the sequence set forth in SEQ ID NO:107.

The term "proline-rich region" as used herein, refers to a region of a protein kinase whose proline content over a given amino acid length is higher than the average content of this amino acid found in proteins(*i.e.*, >10%). Proline-rich regions are easily discernable by visual inspection of amino acid sequences and quantitated by standard computer sequence analysis programs such as the DNAStar program EditSeq. Proline-rich regions have been demonstrated to participate in regulatory protein -protein interactions. Among these interactions, those that are most relevant to this invention involve the "PxxP" proline rich motif found in certain protein kinases (*i.e.*, human PAK1) and the SH3 domain of the adaptor molecule Nck (Galisteo, M.L. *et al.* (1996) J. Biol. Chem. 271:20997-21000). Other regulatory interactions involving "PxxP" proline-rich motifs include the WW domain (Sudol, M. (1996) Prog. Biochys. Mol. Bio. 65:113-132).

The proline-rich region spans amino acid residues 527-640 of the sequence set forth in SEQ ID NO:13, residues 443-626 of the sequence set forth in SEQ ID NO:14, residues 477-680 of the sequence set forth in SEQ ID NO:15, residues 347-534 of the sequence set forth in SEQ ID NO:18,residues 398-628 of the sequence set forth in SEQ ID NO:105, or residues 338-472 of the sequence set forth in SEQ ID NO:107.

The term "spacer region" as used herein, refers to a region of the protein kinase located between predicted functional domains. The spacer region has no detectable

homology to any amino acid sequence in the database, and can be identified by using a Smith-Waterman alignment of the protein sequence against the non-redundant protein database to define the C- and N-terminal boundaries of the flanking functional domains. Spacer regions may or may not play a fundamental role in protein kinase function. Precedence for the regulatory role of spacer regions in kinase function is provided by the role of the src kinase spacer in inter-domain interactions (Xu, W. *et al.* (1997) Nature 385:595-602).

The spacer region spans amino acid residues 641-896 of the sequence set forth in SEQ ID NO:13, residues 627-954 of the sequence set forth in SEQ ID NO:14, residues 681-983 of the sequence set forth in SEQ ID NO:15, residues 274-346 of the sequence set forth in SEQ ID NO:18, residues 278-427 or 638-751 of the sequence set forth in SEQ ID NO:22, residues 67-215 or 426-539 of the sequence set forth in SEQ ID NO:23, residues 274-422 or 633-748 of the sequence set forth in SEQ ID NO:24, residues 225-393 of the sequence set forth in SEQ ID NO:29, residues 282-430 or 641-754 of the sequence set forth in SEQ ID NO:31, residues 174-307 of the sequence set forth in SEQ ID NO:103, residues 669-872 of the sequence set forth in SEQ ID NO:105, or residues 295-337 of the sequence set forth in SEQ ID NO:107.

The term "insert" as used herein refers to a portion of a protein kinase that is absent from a close homolog. Inserts may or may not by the product alternative splicing of exons. Inserts can be identified by using a Smith-Waterman sequence alignment of the protein sequence against the non-redundant protein database, or by means of a multiple sequence alignment of homologous sequences using the DNAStar program Megalign. Inserts may play a functional role by presenting a new interface for protein-protein

interactions, or by interfering with such interactions. Inserts span amino acid residues 52-224 of the sequence set forth in SEQ ID NO:29 or residues 53-173 of the sequence set forth in SEQ ID NO:103.

The term "C-terminal tail" as used herein, refers to a C-terminal domain of a protein kinase, that by homology extends or protrudes past the C-terminal amino acid of its closest homolog. C-terminal tails can be identified by using a Smith-Waterman sequence alignment of the protein sequence against the non-redundant protein database, or by means of a multiple sequence alignment of homologous sequences using the DNAStar program Megalign. Depending on its length, a C-terminal tail may or may not play a regulatory role in kinase function.

The C-terminal tail spans amino acid residues 490-516 of the sequence set forth in SEQ ID NO:6, residues 787-887 of the sequence set forth in SEQ ID NO:23, residues 659-681 of the sequence set forth in SEQ ID NO:29, residues 994-1093 of the sequence set forth in SEQ ID NO:31, or residues 573-591 of the sequence set forth in SEQ ID NO:103.

Various low or high stringency hybridization conditions may be used depending upon the specificity and selectivity desired. These conditions are well-known to those skilled in the art. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. Preferably, such conditions prevent hybridization of nucleic acids having more than 1 or 2 mismatches out of 20 contiguous nucleotides, more preferably, such conditions prevent hybridization of nucleic acids having more than 1 or 2 mismatches out of 50 contiguous nucleotides, most preferably, such conditions prevent hybridization of nucleic acids having more than 1 or 2 mismatches out of 100 contiguous nucleotides. In some instances, the conditions

may prevent hybridization of nucleic acids having more than 5 mismatches in the full-length sequence.

By stringent hybridization assay conditions is meant hybridization assay conditions at least as stringent as the following: hybridization in 50% formamide, 5X SSC, 50 mM NaH_2PO_4, pH 6.8, 0.5% SDS, 0.1 mg/mL sonicated salmon sperm DNA, and 5X Denhart solution at 42 °C overnight; washing with 2X SSC, 0.1% SDS at 45 °C; and washing with 0.2X SSC, 0.1% SDS at 45 °C. Under some of the most stringent hybridization assay conditions, the second wash can be done with 0.1X SSC at a temperature up to 70 °C (Berger et al. (1987) Guide to Molecular Cloning Techniques pg 421, hereby incorporated by reference herein including any figures, tables, or drawings.). However, other applications may require the use of conditions falling between these sets of conditions. Methods of determining the conditions required to achieve desired hybridizations are well-known to those with ordinary skill in the art, and are based on several factors, including but not limited to, the sequences to be hybridized and the samples to be tested.

In other preferred embodiments, the invention features isolated, enriched, or purified nucleic acid molecules encoding kinase polypeptides, further comprising a vector or promoter effective to initiate transcription in a host cell. The invention also features recombinant nucleic acid, preferably in a cell or an organism. The recombinant nucleic acid may contain a sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102,SEQ ID NO:104, or SEQ ID NO:106, or a functional derivative thereof and a vector or a promoter effective to initiate transcription in a host cell. The

recombinant nucleic acid can alternatively contain a transcriptional initiation region functional in a cell, a sequence complementary to an RNA sequence encoding a kinase polypeptide and a transcriptional termination region functional in a cell. Specific vectors and host cell combinations are discussed herein.

The term "vector" relates to a single or double-stranded circular nucleic acid molecule that can be transfected into cells and replicated within or independently of a cell genome. A circular double-stranded nucleic acid molecule can be cut and thereby linearized upon treatment with restriction enzymes. An assortment of nucleic acid vectors, restriction enzymes, and the knowledge of the nucleotide sequences cut by restriction enzymes are readily available to those skilled in the art. A nucleic acid molecule encoding a kinase can be inserted into a vector by cutting the vector with restriction enzymes and ligating the two pieces together.

The term "transfecting" defines a number of methods to insert a nucleic acid vector or other nucleic acid molecules into a cellular organism. These methods involve a variety of techniques, such as treating the cells with high concentrations of salt, an electric field, detergent, or DMSO to render the outer membrane or wall of the cells permeable to nucleic acid molecules of interest or use of various viral transduction strategies.

The term "promoter" as used herein, refers to nucleic acid sequence needed for gene sequence expression. Promoter regions vary from organism to organism, but are well known to persons skilled in the art for different organisms. For example, in prokaryotes, the promoter region contains both the promoter (which directs the initiation of RNA transcription) as well as the DNA sequences which, when

transcribed into RNA, will signal synthesis initiation. Such regions will normally include those 5'-non-coding sequences involved with initiation of transcription and translation, such as the TATA box, capping sequence, CAAT sequence, and the like.

In preferred embodiments, the isolated nucleic acid comprises, consists essentially of, or consists of a nucleic acid sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100 SEQ ID NO:102, SEQ ID NO:104, or SEQ ID NO:106, or the corresponding full-length sequence, encodes the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, a functional derivative thereof, or at least 40, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or of the corresponding full-length amino acid sequence; at least 250, 255, 275, 300, or 400 contiguous amino acids of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or of the corresponding full-length amino acid sequence; at least 27, 30, 35, 40, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:18; at least 16, 25, 35, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, or SEQ ID NO:103, or of the corresponding full-length amino acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, or the corresponding full-

length amino acid sequence; 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101, or the corresponding full-length amino acid sequence; or at least 80, 85, 90, 100, 200, or 300 contiguous amino acids of SEQ ID NO:107, or functional derivatives thereof. The kinase polypeptides, selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, comprise, consist essentially of, or consist of at least at least 40, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7; at least 250, 255, 275, 300, or 400 contiguous amino acids of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:105; at least 27, 30, 35, 40, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:18; at least 35, 40, 45, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31 or SEQ ID NO:103; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99; 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101; or at least 80, 85, 90, 100, 200, or 300 contiguous amino acids of SEQ ID NO:107, or the corresponding full-length sequences or derivatives thereof. The nucleic acid may be isolated from a natural source by cDNA cloning or by subtractive hybridization. The natural source may be mammalian, preferably human, blood, semen, or tissue, and the nucleic acid may be synthesized by the triester method or by using an automated DNA synthesizer.

The term "mammal" refers preferably to such organisms as mice, rats, rabbits, guinea pigs, sheep, and goats, more

preferably to cats, dogs, monkeys, and apes, and most preferably to humans.

In yet other preferred embodiments, the nucleic acid is a conserved or unique region, for example those useful for: the design of hybridization probes to facilitate identification and cloning of additional polypeptides, the design of PCR probes to facilitate cloning of additional polypeptides, obtaining antibodies to polypeptide regions, and designing antisense oligonucleotides.

By "conserved nucleic acid regions", are meant regions present on two or more nucleic acids encoding a kinase polypeptide, to which a particular nucleic acid sequence can hybridize under lower stringency conditions. Examples of lower stringency conditions suitable for screening for nucleic acid encoding kinase polypeptides are provided in Abe, *et al.* (J. Biol. Chem. 19:13361-13368, 1992), hereby incorporated by reference herein in its entirety, including any drawings, figures, or tables. Preferably, conserved regions differ by no more than 5 out of 20 nucleotides, even more preferably 2 out of 20 nucleotides or most preferably 1 out of 20 nucleotides.

By "unique nucleic acid region" is meant a sequence present in a nucleic acid coding for a kinase polypeptide that is not present in a sequence coding for any other naturally occurring polypeptide. Such regions preferably encode 32 (preferably 40, more preferably 45, most preferably 55) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or the corresponding full-length amino acid sequence; 250 (preferably 255, more preferably 260, most preferably 270) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15, or SEQ ID NO:105, or the corresponding full-length

amino acid sequence; 27 (preferably 30, more preferably 40, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:18; 16 (preferably 20, more preferably 25, most preferably 35) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, or SEQ ID NO:103, or the corresponding full-length amino acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101, or the corresponding full-length amino acid sequence; or 78 (preferably 80, more preferably 85, most preferably 90) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:107, or functional derivatives thereof. In particular, a unique nucleic acid region is preferably of mammalian origin.

A second aspect of the invention features a nucleic acid probe for the detection of nucleic acid encoding a kinase polypeptide in a sample, wherein said polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. Preferably, the nucleic acid probe encodes a kinase polypeptide that is a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequences, not to include fragments consisting only of amino acids 1-22 of SEQ ID NO:13 or amino acids 1-33

of SEQ ID NO:107. The nucleic acid probe contains a nucleotide base sequence that will hybridize to a sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, or SEQ ID NO:106, or the corresponding full-length sequence, or a functional derivative thereof.

In preferred embodiments, the nucleic acid probe hybridizes to nucleic acid encoding at least 6, 12, 75, 90, 105, 120, 150, 200, 250, 300 or 350 contiguous amino acids of the sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31 SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, or functional derivatives thereof.

Methods for using the probes include detecting the presence or amount of kinase RNA in a sample by contacting the sample with a nucleic acid probe under conditions such that hybridization occurs and detecting the presence or amount of the probe bound to kinase RNA. The nucleic acid duplex formed between the probe and a nucleic acid sequence coding for a kinase polypeptide may be used in the identification of the sequence of the nucleic acid detected (Nelson *et al.*, in Nonisotopic DNA Probe Techniques, Academic Press, San Diego, Kricka, ed., p. 275, 1992, hereby incorporated by reference herein in its entirety, including any drawings, figures, or tables). Kits for performing such methods may be constructed to include a container means having disposed therein a nucleic acid probe.

In a third aspect, the invention describes a recombinant cell or tissue comprising a nucleic acid molecule encoding a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. In such cells, the nucleic acid may be under the control of the genomic regulatory elements, or may be under the control of exogenous regulatory elements including an exogenous promoter. By "exogenous" it is meant a promoter that is not normally coupled *in vivo* transcriptionally to the coding sequence for the kinase polypeptides.

The polypeptide is preferably a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, not to include fragments consisting only of amino acids 1-22 of SEQ ID NO:13 or amino acids 1-33 of SEQ ID NO:107. By "fragment," is meant an amino acid sequence present in a kinase polypeptide. Preferably, such a sequence comprises at least 32, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or of the corresponding full-length amino acid sequence; at least 250, 255, 275, 300, or 400 contiguous amino acids of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, OR SEQ ID NO:105, or of the corresponding full-length amino acid sequence; at least 27, 30, 35, 40, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:18; at least 16, 25, 35, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31 or SEQ ID NO:103, or of the corresponding full-length amino

acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101; at least 78, 85, 90, 100, 200, or 300 contiguous amino acids of SEQ ID NO:107, or the corresponding full-length amino acid sequence; or a functional derivative thereof.

In a fourth aspect, the invention features an isolated, enriched, or purified kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

By "isolated" in reference to a polypeptide is meant a polymer of amino acids (2 or more amino acids) conjugated to each other, including polypeptides that are isolated from a natural source or that are synthesized. The isolated polypeptides of the present invention are unique in the sense that they are not found in a pure or separated state in nature. Use of the term "isolated" indicates that a naturally occurring sequence has been removed from its normal cellular environment. Thus, the sequence may be in a cell-free solution or placed in a different cellular environment. The term does not imply that the sequence is the only amino acid chain present, but that it is essentially free (about 90 - 95% pure at least) of non-amino acid material naturally associated with it.

By the use of the term "enriched" in reference to a polypeptide is meant that the specific amino acid sequence constitutes a significantly higher fraction (2 - 5 fold) of the total amino acid sequences present in the cells or solution of interest than in normal or diseased cells or in

the cells from which the sequence was taken. This could be caused by a person by preferential reduction in the amount of other amino acid sequences present, or by a preferential increase in the amount of the specific amino acid sequence of interest, or by a combination of the two. However, it should be noted that enriched does not imply that there are no other amino acid sequences present, just that the relative amount of the sequence of interest has been significantly increased. The term significant here is used to indicate that the level of increase is useful to the person making such an increase, and generally means an increase relative to other amino acid sequences of about at least 2-fold, more preferably at least 5- to 10-fold or even more. The term also does not imply that there is no amino acid sequence from other sources. The other source of amino acid sequences may, for example, comprise amino acid sequence encoded by a yeast or bacterial genome, or a cloning vector such as pUC19. The term is meant to cover only those situations in which man has intervened to increase the proportion of the desired amino acid sequence.

It is also advantageous for some purposes that an amino acid sequence be in purified form. The term "purified" in reference to a polypeptide does not require absolute purity (such as a homogeneous preparation); instead, it represents an indication that the sequence is relatively purer than in the natural environment. Compared to the natural level this level should be at least 2-5 fold greater (*e.g.*, in terms of mg/mL). Purification of at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated. The substance is preferably free of contamination at a functionally significant level, for example 90%, 95%, or 99% pure.

In preferred embodiments, the kinase polypeptide is a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequences, not to include fragments consisting only of amino acids 1-22 of SEQ ID NO:13 or amino acids 1-33 of SEQ ID NO:107. Preferably, the kinase polypeptide contains at least 32, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or the corresponding full-length amino acid sequence; at least 250, 255, 275, 300, or 400 contiguous amino acids of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:105, or the corresponding full-length amino acid sequence; at least 27, 30, 35, 40, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:18; at least 16, 25, 35, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, or SEQ ID NO:103, or the corresponding full-length amino acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101, or the corresponding full-length amino acid sequence; or at least 78, 85, 90, 100, 200, or 300 contiguous amino acids of SEQ ID NO:107, or a functional derivative thereof.

In preferred embodiments, the kinase polypeptide comprises an amino acid sequence having (a) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7,

SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107; (b) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, except that it lacks one or more, but not all, of the following segments of amino acid residues: 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489 or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 1-22, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 282-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID NO:103, 1-24, 25-289, 290-397, 398-628, 629-668, 669-872, or 873-1227 of SEQ ID NO:105, or 1-33, 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107; (c) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107 from amino acid residues 1-21, 22-274, or 275-416 of

SEQ ID NO:5, 1-31, 32-308, 309-489, or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-273, 274-422, 423-632, 633-746, 747-993, or 994-1093 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID NO:103, 1-24, 25-289, 290-397, 398-628, 629-668, 669-872, or 873-1227 of SEQ ID NO:105, or 1-33, 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107; or (d) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, except that it lacks one or more, but not all, of the domains selected from the group consisting of a C-terminal domain, a catalytic domain, an N-terminal domain, a spacer region, a proline-rich region, a coiled-coil structure region, an insert, and a C-terminal tail.

The polypeptide can be isolated from a natural source by methods well-known in the art. The natural source may be mammalian, preferably human, blood, semen, or tissue, and the polypeptide may be synthesized using an automated polypeptide synthesizer. The isolated, enriched, or purified kinase polypeptide is preferably: a STLK2, STLK3,

STLK4, STLK5, STLK6, or STLK7 polypeptide; a ZC1, ZC2, ZC3, or ZC4 polypeptide; a KHS2 polypeptide; a SULU1 or SULU3 polypeptide; a GEK2 polypeptide; or a PAK4 or PAK5 polypeptide.

In some embodiments the invention includes a recombinant kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. By "recombinant kinase polypeptide" is meant a polypeptide produced by recombinant DNA techniques such that it is distinct from a naturally occurring polypeptide either in its location (*e.g.*, present in a different cell or tissue than found in nature), purity or structure. Generally, such a recombinant polypeptide will be present in a cell in an amount different from that normally observed in nature.

In a fifth aspect, the invention features an antibody (*e.g.*, a monoclonal or polyclonal antibody) having specific binding affinity to a kinase polypeptide or a kinase polypeptide domain or fragment where the polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. By "specific binding affinity" is meant that the antibody binds to the target kinase polypeptide with greater affinity than it binds to other polypeptides under specified conditions. Antibodies or antibody fragments are polypeptides that contain regions that can bind other polypeptides. The term "specific binding affinity" describes an antibody that binds to a kinase polypeptide with greater affinity than it binds to other polypeptides under specified conditions.

The term "polyclonal" refers to antibodies that are heterogenous populations of antibody molecules derived from the sera of animals immunized with an antigen or an

antigenic functional derivative thereof. For the production of polyclonal antibodies, various host animals may be immunized by injection with the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species.

"Monoclonal antibodies" are substantially homogenous populations of antibodies to a particular antigen. They may be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. Monoclonal antibodies may be obtained by methods known to those skilled in the art (Kohler et al., Nature 256:495-497, 1975, and U.S. Patent No. 4,376,110, both of which are hereby incorporated by reference herein in their entirety including any figures, tables, or drawings).

The term "antibody fragment" refers to a portion of an antibody, often the hyper variable region and portions of the surrounding heavy and light chains, that displays specific binding affinity for a particular molecule. A hyper variable region is a portion of an antibody that physically binds to the polypeptide target.

Antibodies or antibody fragments having specific binding affinity to a kinase polypeptide of the invention may be used in methods for detecting the presence and/or amount of kinase polypeptide in a sample by probing the sample with the antibody under conditions suitable for kinase-antibody immunocomplex formation and detecting the presence and/or amount of the antibody conjugated to the kinase polypeptide. Diagnostic kits for performing such methods may be constructed to include antibodies or antibody fragments specific for the kinase as well as a conjugate of a binding partner of the antibodies or the antibodies themselves.

An antibody or antibody fragment with specific binding affinity to a kinase polypeptide of the invention can be isolated, enriched, or purified from a prokaryotic or eukaryotic organism. Routine methods known to those skilled in the art enable production of antibodies or antibody fragments, in both prokaryotic and eukaryotic organisms. Purification, enrichment, and isolation of antibodies, which are polypeptide molecules, are described above.

Antibodies having specific binding affinity to a kinase polypeptide of the invention may be used in methods for detecting the presence and/or amount of kinase polypeptide in a sample by contacting the sample with the antibody under conditions such that an immunocomplex forms and detecting the presence and/or amount of the antibody conjugated to the kinase polypeptide. Diagnostic kits for performing such methods may be constructed to include a first container containing the antibody and a second container having a conjugate of a binding partner of the antibody and a label, such as, for example, a radioisotope. The diagnostic kit may also include notification of an FDA approved use and instructions therefor.

In a sixth aspect, the invention features a hybridoma which produces an antibody having specific binding affinity to a kinase polypeptide or a kinase polypeptide domain, where the polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. By "hybridoma" is meant an immortalized cell line that is capable of secreting an antibody, for example an antibody to a kinase of the invention. In preferred embodiments, the antibody to the kinase comprises a sequence of amino acids that is able to specifically bind a kinase polypeptide of the invention.

In a seventh aspect, the invention features a kinase polypeptide binding agent able to bind to a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK6, STLK7, STLK5, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. The binding agent is preferably a purified antibody that recognizes an epitope present on a kinase polypeptide of the invention. Other binding agents include molecules that bind to kinase polypeptides and analogous molecules that bind to a kinase polypeptide. Such binding agents may be identified by using assays that measure kinase binding partner activity, such as those that measure PDGFR activity.

The invention also features a method for screening for human cells containing a kinase polypeptide of the invention or an equivalent sequence. The method involves identifying the novel polypeptide in human cells using techniques that are routine and standard in the art, such as those described herein for identifying the kinases of the invention (*e.g.*, cloning, Southern or Northern blot analysis, in situ hybridization, PCR amplification, etc.).

In an eighth aspect, the invention features methods for identifying a substance that modulates kinase activity comprising the steps of: (a) contacting a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5 with a test substance; (b) measuring the activity of said polypeptide; and (c) determining whether said substance modulates the activity of said polypeptide.

The term "modulates" refers to the ability of a compound to alter the function of a kinase of the invention. A modulator preferably activates or inhibits the activity

of a kinase of the invention depending on the concentration of the compound exposed to the kinase.

The term "activates" refers to increasing the cellular activity of the kinase. The term inhibit refers to decreasing the cellular activity of the kinase. Kinase activity is preferably the interaction with a natural binding partner.

The term "modulates" also refers to altering the function of kinases of the invention by increasing or decreasing the probability that a complex forms between the kinase and a natural binding partner. A modulator preferably increases the probability that such a complex forms between the kinase and the natural binding partner, more preferably increases or decreases the probability that a complex forms between the kinase and the natural binding partner depending on the concentration of the compound exposed to the kinase, and most preferably decreases the probability that a complex forms between the kinase and the natural binding partner.

The term "complex" refers to an assembly of at least two molecules bound to one another. Signal transduction complexes often contain at least two protein molecules bound to one another. For instance, a protein tyrosine receptor protein kinase, GRB2, SOS, RAF, and RAS assemble to form a signal transduction complex in response to a mitogenic ligand.

The term "natural binding partner" refers to polypeptides, lipids, small molecules, or nucleic acids that bind to kinases in cells. A change in the interaction between a kinase and a natural binding partner can manifest itself as an increased or decreased probability that the interaction forms, or an increased or decreased concentration of kinase/natural binding partner complex.

The term "contacting" as used herein refers to mixing a solution comprising the test compound with a liquid medium bathing the cells of the methods. The solution comprising the compound may also comprise another component, such as dimethyl sulfoxide (DMSO), which facilitates the uptake of the test compound or compounds into the cells of the methods. The solution comprising the test compound may be added to the medium bathing the cells by utilizing a delivery apparatus, such as a pipet-based device or syringe-based device.

In a ninth aspect, the invention features methods for identifying a substance that modulates kinase activity in a cell comprising the steps of: (a) expressing a kinase polypeptide in a cell, wherein said polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5; (b) adding a test substance to said cell; and (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

The term "expressing" as used herein refers to the production of kinases of the invention from a nucleic acid vector containing kinase genes within a cell. The nucleic acid vector is transfected into cells using well known techniques in the art as described herein.

In a tenth aspect, the invention provides methods for treating a disease by administering to a patient in need of such treatment a substance that modulates the activity of a kinase selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. Preferably, the disease is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial

infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer. Most preferably, the immune-related diseases and disorders include, but are not limited to, rheumatoid arthritis, artherosclerosis, and autoimmune disorders.

In preferred embodiments, the invention provides methods for treating or preventing a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a kinase polypeptide selected from the group consisting of ZC1, ZC2, ZC3, ZC4, KHS2, PAK4, and PAK5. Preferably, the disease or disorder is selected from the group consisting of rheumatoid arthritis, artherosclerosis, autoimmune disorders, and organ transplantation. The invention also features methods of treating or preventing a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a kinase polypeptide selected from the group consisting of STLK1, STLK2, STLK3, STLK4, STLK5, STLK6, and STLK7. Preferably the disease or disorder is selected from the group consisting of immune-related diseases and disorders, myocardial infarction, cardiomyopathies, stroke, renal failure, and oxidative stress-related neurodegenerative disorders. Most preferably, the immune-related diseases and disorders are selected from the group consisting of rheumatoid arthritis, chronic inflammatory bowel disease, chronic inflammatory pelvic disease, multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis, autoimmunity, and organ transplantation.

The invention also features methods of treating or preventing a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a kinase polypeptide selected from the group

consisting of ZC1, ZC2, ZC3, and ZC4. Preferably the disease is selected from the group consisting of immune-related diseases and disorders, cardiovascular disease, and cancer. Most preferably, the immune-related diseases and disorders are selected from the group consisting of rheumatoid arthritis, chronic inflammatory bowel disease, chronic inflammatory pelvic disease, multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis, autoimmunity, and organ transplantation.

Substances useful for treatment of kinase-related disorders or diseases preferably show positive results in one or more *in vitro* assays for an activity corresponding to treatment of the disease or disorder in question (Examples of such assays are provided in the references in section VI, below; and in Example 7, herein). Examples of substances that can be screened for favorable activity are provided and referenced in section VI, below. The substances that modulate the activity of the kinases preferably include, but are not limited to, antisense oligonucleotides and inhibitors of protein kinases, as determined by methods and screens referenced in section VI and Example 7, below.

The term "preventing" refers to decreasing the probability that an organism contracts or develops an abnormal condition.

The term "treating" refers to having a therapeutic effect and at least partially alleviating or abrogating an abnormal condition in the organism.

The term "therapeutic effect" refers to the inhibition or activation factors causing or contributing to the abnormal condition. A therapeutic effect relieves to some extent one or more of the symptoms of the abnormal condition. In reference to the treatment of abnormal conditions, a therapeutic effect can refer to one or more of

the following: (a) an increase in the proliferation, growth, and/or differentiation of cells; (b) inhibition (*i.e.*, slowing or stopping) of cell death; (c) inhibition of degeneration; (d) relieving to some extent one or more of the symptoms associated with the abnormal condition; and (e) enhancing the function of the affected population of cells. Compounds demonstrating efficacy against abnormal conditions can be identified as described herein.

The term "abnormal condition" refers to a function in the cells or tissues of an organism that deviates from their normal functions in that organism. An abnormal condition can relate to cell proliferation, cell differentiation, or cell survival.

Abnormal cell proliferative conditions include cancers such as fibrotic and mesangial disorders, abnormal angiogenesis and vasculogenesis, wound healing, psoriasis, diabetes mellitus, and inflammation.

Abnormal differentiation conditions include, but are not limited to neurodegenerative disorders, slow wound healing rates, and slow tissue grafting healing rates.

Abnormal cell survival conditions relate to conditions in which programmed cell death (apoptosis) pathways are activated or abrogated. A number of protein kinases are associated with the apoptosis pathways. Aberrations in the function of any one of the protein kinases could lead to cell immortality or premature cell death.

The term "aberration", in conjunction with the function of a kinase in a signal transduction process, refers to a kinase that is over- or under-expressed in an organism, mutated such that its catalytic activity is lower or higher than wild-type protein kinase activity, mutated such that it can no longer interact with a natural binding partner, is no longer modified by another protein kinase or protein

phosphatase, or no longer interacts with a natural binding partner.

The term "administering" relates to a method of incorporating a compound into cells or tissues of an organism. The abnormal condition can be prevented or treated when the cells or tissues of the organism exist within the organism or outside of the organism. Cells existing outside the organism can be maintained or grown in cell culture dishes. For cells harbored within the organism, many techniques exist in the art to administer compounds, including (but not limited to) oral, parenteral, dermal, injection, and aerosol applications. For cells outside of the organism, multiple techniques exist in the art to administer the compounds, including (but not limited to) cell microinjection techniques, transformation techniques, and carrier techniques.

The abnormal condition can also be prevented or treated by administering a compound to a group of cells having an aberration in a signal transduction pathway to an organism. The effect of administering a compound on organism function can then be monitored. The organism is preferably a mouse, rat, rabbit, guinea pig, or goat, more preferably a monkey or ape, and most preferably a human.

In an eleventh aspect, the invention features methods for detection of a kinase polypeptide in a sample as a diagnostic tool for diseases or disorders, wherein the method comprises the steps of: (a) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a nucleic acid target region of a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, said probe comprising the nucleic acid sequence encoding the

polypeptide, fragments thereof, and the complements of the sequences and fragments; and (b) detecting the presence or amount of the probe:target region hybrid as an indication of the disease.

In preferred embodiments of the invention, the disease or disorder is selected from the group consisting of rheumatoid arthritis, artherosclerosis, autoimmune disorders, organ transplantation, myocardial infarction, cardiomyopathies, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer. In other preferred embodiments, the kinase polypeptide is selected from the group consisting of PAK4 and PAK5, or the polypeptide is selected from the group consisting of ZC1, ZC2, ZC3, and ZC4, and the disease is cancer.

The kinase "target region" is the nucleotide base sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, or SEQ ID NO:106, or the corresponding full-length sequences, a functional derivative thereof, or a fragment thereof to which the nucleic acid probe will specifically hybridize. Specific hybridization indicates that in the presence of other nucleic acids the probe only hybridizes detectably with the kinase of the invention's target region. Putative target regions can be identified by methods well known in the art consisting of alignment and comparison of the most closely related sequences in the database.

In preferred embodiments the nucleic acid probe hybridizes to a kinase target region encoding at least 6, 12, 75, 90, 105, 120, 150, 200, 250, 300 or 350 contiguous amino acids of the sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15,

SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, or a functional derivative thereof. Hybridization conditions should be such that hybridization occurs only with the kinase genes in the presence of other nucleic acid molecules. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. Preferably, such conditions prevent hybridization of nucleic acids having more than 1 or 2 mismatches out of 20 contiguous nucleotides. Such conditions are defined supra.

The diseases for which detection of kinase genes in a sample could be diagnostic include diseases in which kinase nucleic acid (DNA and/or RNA) is amplified in comparison to normal cells. By "amplification" is meant increased numbers of kinase DNA or RNA in a cell compared with normal cells. In normal cells, kinases are typically found as single copy genes. In selected diseases, the chromosomal location of the kinase genes may be amplified, resulting in multiple copies of the gene, or amplification. Gene amplification can lead to amplification of kinase RNA, or kinase RNA can be amplified in the absence of kinase DNA amplification.

"Amplification" as it refers to RNA can be the detectable presence of kinase RNA in cells, since in some normal cells there is no basal expression of kinase RNA. In other normal cells, a basal level of expression of kinase exists, therefore in these cases amplification is the detection of at least 1-2-fold, and preferably more, kinase RNA, compared to the basal level.

The diseases that could be diagnosed by detection of kinase nucleic acid in a sample preferably include cancers. The test samples suitable for nucleic acid probing methods

of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well known in the art and can be readily adapted in order to obtain a sample that is compatible with the method utilized.

In a final aspect, the invention features a method for detection of a kinase polypeptide in a sample as a diagnostic tool for a disease or disorder, wherein the method comprises: (a) comparing a nucleic acid target region encoding the kinase polypeptide in a sample, where the kinase polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, or one or more fragments thereof, with a control nucleic acid target region encoding the kinase polypeptide, or one or more fragments thereof; and (b) detecting differences in sequence or amount between the target region and the control target region, as an indication of the disease or disorder. Preferably, the disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer. Immune-related diseases and disorders include, but are not limited to, those discussed previously.

The term "comparing" as used herein refers to identifying discrepancies between the nucleic acid target region isolated from a sample, and the control nucleic acid target region. The discrepancies can be in the nucleotide sequences, *e.g.* insertions, deletions, or point mutations,

or in the amount of a given nucleotide sequence. Methods to determine these discrepancies in sequences are well-known to one of ordinary skill in the art. The "control" nucleic acid target region refers to the sequence or amount of the sequence found in normal cells, *e.g.* cells that are not diseased as discussed previously.

The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein. For example, in some instances the nucleotide sequence of the ZC4 kinase polypeptide may not be part of a preferred embodiment.

The summary of the invention described above is not limiting and other features and advantages of the invention will be apparent from the following detailed description of the invention, and from the claims.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a multiple sequence alignment of the amino acid sequences of the STE20-STE20 family kinases.

Figure 2 shows a multiple sequence alignment of the amino acid sequences of the STE20-STLK5 family kinases.

Figures 3A and 3B show a multiple sequence alignment of the amino acid sequences of STE20-ZC family kinases.

Figure 4 shows a pairwise sequence alignment of STE20-KHS family kinases.

Figure 5 shows a multiple sequence alignment of the amino acid sequences of STE20-SULU family kinases.

Figure 6 shows a pairwise sequence alignment of STE20-GEK family kinases

Figure 7 shows a multiple sequence alignment of the amino acid sequences of STE20-PAK family kinases.

Figures 8A, 8B, 8C, 8D, and 8E show the amino acid sequences of human STLK2, human STLK3, human STLK4, human STLK5, human ZC1, human ZC2, human ZC3, human ZC4, human KHS2, human SULU1, human SULU3, murine SULU3, human GEK2, human PAK4, and human PAK5.

Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, 9I, 9J, 9K, 9L, 9M, 9N, 9O, and 9P show the nucleic acid sequences of human STLK2, human STLK3, human STLK4, human STLK5, human ZC1, human ZC2, human ZC3, human ZC4, human KHS2, human SULU1, human SULU3, murine SULU3, human GEK2, human PAK4, and human PAK5.

Figures 10A and 10B show the full-length amino acid sequences of human STLK5 (SEQ ID NO: 97), human PAK5 (SEQ ID NO:103), and human ZC4 (SEQ ID NO:105), as well as the partial amino acid sequences of human full-length STLK6 (SEQ ID NO: 99) and human STLK7 (SEQ ID NO: 101).

Figures 11A, 11B, 11C, and 11D show the full-length nucleic acid sequences of human STLK5 (SEQ ID NO:96), human PAK5 (SEQ ID NO:102), and human ZC4 (SEQ ID NO:104), as well as the partial nucleic acid sequences of human STLK6 (SEQ ID NO: 98) and human STLK7 (SEQ ID NO: 100).

Figure 12 shows a multiple sequence alignment among human SPAK, human STLK6, human STLK7 and full-length human STLK5.

Figure 13 shows a multiple sequence alignment among human PAK1, human PAK4 and human PAK5.

Figures 14A and 14B show a pair-wise sequence alignment between human ZC1 and human ZC4.

Figure 15 shows a pair-wise sequence alignment between LOK1 and full-length GEK2.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates in part to kinase polypeptides, nucleic acids encoding such polypeptides, cells containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. The present invention is based upon the isolation and characterization of new kinase polypeptides. The polypeptides and nucleic acids may be produced using well-known and standard synthesis techniques when given the sequences presented herein.

The recent elucidation of the DNA sequence of *Saccharomyces cerevesiae* has provided the first complete example of the genetic information contained in a simple eukaryotic organism. Analysis of this yeast genome revealed that it contains at least 113 protein kinases. These kinases were further subdivided into several structurally related groups. One of these newly defined groups was termed the STE20-family to represent its founding member STE20, which is a protein kinase involved in the yeast pheromone response pathway that initiates a protein kinase cascade in response to a G-protein mediated signal. *S. cerevesiae* has two additional members of this family, CLA4, and YOL113W (HRA655).

Several mammalian homologues have recently been identified that belong to the STE20-family, including SOK-1 (human STE20), GC-kinase, KHS, HPK1, NIK, SLK, GEK, PAK1, PAK65, MST1, and CDC7. Furthermore, the *Drosophila* and the *C. elegans* genome efforts have identified additional protein kinases which belong to the STE20-family, yet have

structurally unique extracatalytic domains, including ZC504.4 and SULU kinases from *C. elegans*, and NINAC of *Drosophila*.

STE20-related protein kinases have been implicated as regulating a variety of cellular responses, including response to growth factors or cytokines, oxidative-, UV-, or irradiation-related stress pathways, inflammatory signals (*i.e.*, TNFα), apoptotic stimuli (*i.e.*, Fas), T and B cell costimulation, the control of cytoskeletal architecture, and cellular transformation. Typically, the STE20-related kinases serve as upstream regulators of MAPK cascades. Examples include: HPK1, a protein-serine/ threonine kinase (STK) that possesses a STE20-like kinase domain that activates a protein kinase pathway leading to the stress-activated protein kinase SAPK/JNK; PAK1, an STK with an upstream CDC42-binding domain that interacts with Rac and plays a role in cellular transformation through the Ras-MAPK pathway; and murine NIK, which interacts with upstream receptor tyrosine kinases and connects with downstream STE11-family kinases.

The STE20-kinases possess a variety of non-catalytic domains that are believed to interact with upstream regulators. Examples include proline-rich domains for interaction with SH3-containing proteins, or specific domains for interaction with Rac, Rho, and Rab small G-proteins. These interactions may provide a mechanism for cross-talk between distinct biochemical pathways in response to external stimuli such as the activation of a variety of cell surface receptors, including tyrosine kinases, cytokine receptors, TNF receptor, Fas, T cell receptors, CD28, or CD40.

I. The Nucleic Acids of the Invention

Included within the scope of this invention are the functional equivalents of the herein-described isolated nucleic acid molecules. The degeneracy of the genetic code permits substitution of certain codons by other codons that specify the same amino acid and hence would give rise to the same protein. The nucleic acid sequence can vary substantially since, with the exception of methionine and tryptophan, the known amino acids can be coded for by more than one codon. Thus, portions or all of the kinase genes of the invention could be synthesized to give a nucleic acid sequence significantly different from that shown in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, and SEQ ID NO:106. The encoded amino acid sequence thereof would, however, be preserved.

In addition, the nucleic acid sequence may comprise a nucleotide sequence which results from the addition, deletion or substitution of at least one nucleotide to the 5'-end and/or the 3'-end of the nucleic acid formula shown in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, or SEQ ID NO:106, or a derivative thereof. Any nucleotide or polynucleotide may be used in this regard, provided that its addition, deletion or substitution does not alter the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID

NO:105, or SEQ ID NO:107, which is encoded by the nucleotide sequence. For example, the present invention is intended to include any nucleic acid sequence resulting from the addition of ATG as an initiation codon at the 5'-end of the inventive nucleic acid sequence or its derivative, or from the addition of TTA, TAG or TGA as a termination codon at the 3'-end of the inventive nucleotide sequence or its derivative. Moreover, the nucleic acid molecule of the present invention may, as necessary, have restriction endonuclease recognition sites added to its 5'-end and/or 3'-end.

Such functional alterations of a given nucleic acid sequence afford an opportunity to promote secretion and/or processing of heterologous proteins encoded by foreign nucleic acid sequences fused thereto. All variations of the nucleotide sequence of the kinase genes of the invention and fragments thereof permitted by the genetic code are, therefore, included in this invention.

Further, it is possible to delete codons or to substitute one or more codons with codons other than degenerate codons to produce a structurally modified polypeptide, but one which has substantially the same utility or activity as the polypeptide produced by the unmodified nucleic acid molecule. As recognized in the art, the two polypeptides are functionally equivalent, as are the two nucleic acid molecules that give rise to their production, even though the differences between the nucleic acid molecules are not related to the degeneracy of the genetic code.

Mammalian STLK2

The full-length human STLK2 cDNA (SEQ ID NO:1) is 3268 bp long and consists of a 1248 bp open reading frame (ORF)

flanked by a 181 bp 5′ untranslated region (UTR; 1-181) and a 1784 bp 3′ UTR (1433-3216) that is followed by a 52 nucleotide polyadenylated region. A polyadenylation signal (AATAAA) is found at positions (3193-3198). The sequence flanking the first ATG conforms to the Kozak consensus (Kozak, M., Nucleic Acids Res. 15, 8125-8148 (1987)) for an initiating methionine, and is believed to be the translational start site for STLK2. Furthermore, human STLK2 and the related SOK-1 and MST3 proteins conserve the amino acid sequence immediately following this presumed initiating methionine.

Several EST fragments span the complete STLK2 sequence with AA191319 at the 5′ end and W16504 at the 3′ end.

Mammalian STLK3

The partial human STLK3 cDNA (SEQ ID NO:2) is 3030 bp long and consists of a 1548 bp ORF flanked by a 1476 bp 3′ UTR (1550-3025) and a 5 nucleotide polyadenylated region. A potential polyadenylation signal (AATAAA) begins at position 3004. Since the coding region is open throughout the 5′ extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine.

Multiple EST fragments span the complete STLK3 sequence with AA278967 at the 5′ end and AA628477 and others at the 3′ end.

Mammalian STLK4

The partial human STLK4 cDNA (SEQ ID NO:3) is 3857 bp long and consists of a 1242 bp ORF flanked by a 2596 bp 3′ UTR (1244-3839) and an 18 nucleotide polyadenylated region. A potential polyadenylation signal (AATAAA) is found at positions 2181-3822. Since the coding region is open throughout the 5′ extent of this sequence, this is

apparently a partial cDNA clone lacking the N-terminal start methionine. A near full-length murine STLK4 cDNA is represented in the 1773 bp EST AA117438. It extends an additional 21 nucleotides 5′ of the human STLK4 consensus, but since its coding region is open throughout the 5′ extent of the sequence, this is also apparently a partial cDNA clone lacking the N-terminal start methionine.

Several EST fragments span the complete STLK3 sequence with AA297759 at the 5′ end and AA100484 and others at the 3′ end.

Mammalian STLK5

The full-length human STLK5 cDNA (SEQ ID NO:96) is 2110 bp long and consists of a 1119 bp ORF flanked by a 229 bp 5' UTR and a 762 bp 3′ UTR. The sequence flanking the first ATG conforms to the Kozak consensus (supra) for an initiating methionine, and is believed to be the translational start site for STLK5. Several EST fragments span the complete STLK5 sequence with AA297059 and F07734 at the 5′ end, and R46686 and F03423 and others at the 3′ end.

Mammalian STLK6

The full-length human STLK6 cDNA (SEQ ID NO:98) is 2,001 bp long and consists of a 1,254 bp ORF flanked by a 75 bp 5' UTR and a 673 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (supra) for an initiating methionine, and is believed to be the translational start site for STLK6.

Mammalian STLK7

The partial human STLK7 cDNA (SEQ ID NO:100) is 311 bp long and consists of a 309 bp ORF. Since the coding region is open throughout both the 5′ and 3′ extent of this

sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine and C-terminal stop codon.

Mammalian ZC1

The full-length human ZC1 cDNA (SEQ ID NO:9) is 3798 bp long and consists of a 3717 bp ORF (7-3723) flanked by a 6 bp 5′ UTR and a 75 bp (3724-3798) 3′ UTR. No polyadenylation signal (AATAAA) or polyadenylated region are present in the 3′UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human ZC1.

Multiple EST fragments (W81656) match the 3′ end of the human ZC1 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5′ end.

Mammalian ZC2

The partial human ZC2 cDNA (SEQ ID NO:10) is 4055 bp long and consists of a 3891 bp ORF (1-3891) and a 164 bp (3892-4055) 3′ UTR. Since the coding region is open throughout the 5′ extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. No polyadenylation signal (AATAAA) or polyadenylated region are present in the 3′UTR.

Multiple EST fragments (R51245) match the 3′ end of the human ZC2 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5′ end.

Mammalian ZC3

The partial human ZC3 cDNA (SEQ ID NO:11) is 4133 bp long and consists of a 3978 bp ORF (1-3978) and a 152 bp

(3979-4133) 3'UTR region. Since the coding region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. No polyadenylation signal (AATAAA) or polyadenylated region are present in the 3'UTR.

Multiple EST fragments (R54563) match the 3'end of the human ZC3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

Mammalian ZC4

The full-length human ZC4 cDNA (SEQ ID NO:104) is 3,684 bp long and was originally assembled from X chromosome genomic DNA sequence.

Multiple EST fragments (R98571) match the 3'end of the human ZC4 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end. ZC4 gene is also contained within the human genomic clone Z83850.

Mammalian KHS2

The full-length human KHS2 cDNA (SEQ ID NO:17) is 4023 bp long and consists of a 2682 bp ORF (6-2687) flanked by a 5 bp (1-5) 5'UTR and a 1336 bp (2688-4023) 3' UTR. A potential polyadenylation signal (AATAAA) is found at positions 4008-4013. No polyadenylated region is present in the 3'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human KHS2.

Multiple EST fragments match the 5'end (AA446022) as well as the 3' end (R37625) of the human KHS2 gene.

Mammalian SULU1

The full-length human SULU1 cDNA (SEQ ID NO:19) is 4177 bp long and consists of a 2694 bp ORF (415-3108) flanked by a 414 bp (1-414) 5'UTR and a 1069 bp (3109-4177) 3' UTR followed by a 19 nucleotide polydenylated region. A potential polyadenylation signal (AATAAA) is found at positions 4164-4169. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human SULU1.

Multiple EST fragments match the 5'end (N27153) as well as the 3' end (R90908) of the human SULU1 gene.

Mammalian (Murine) SULU3

The partial murine SULU3 cDNA (SEQ ID NO:21) is 2249 bp long and consists of a 2244 bp ORF (6-2249) flanked by a 5 bp (1-5) 5'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for murine SULU3. The 3' end of the murine SULU3 cDNA shares 90% DNA sequence identity over 1620 nucleotides with human SULU3, suggesting that these two genes are functional orthologues.

One EST fragment (AA446022) matches the 3' end of the partial murine SULU3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

Mammalian (Human) SULU3

The partial human SULU3 cDNA (SEQ ID NO:20) is 3824 bp long and consists of a 2358 bp ORF (2-2359) flanked by a 1465 bp (2360-3824) 3'UTR followed by a 19 nucleotide polydenylated region. A potential polyadenylation signal

(AATAAA) is found at positions 2602-2607. Since the coding region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. The 5' end of the human SULU3 cDNA shares 90% DNA sequence identity over 1620 nucleotides with murine SULU3, suggesting that these two genes are functional orthologues.

Multiple EST fragments (R02283) match the 3'end of the human SULU3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

Mammalian GEK2

The full-length human GEK2 cDNA (SEQ ID NO:106) is 2962 bp long and consists of a 2737 bp ORF (59-2795) flanked by a 58 bp (1-58) 5'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human GEK2.

Multiple EST fragments (AA465671) match the 5'end, but at the time of filing, the inventors believe that only one (AA380492) matches the 3' end of the human GEK2 gene.

Mammalian PAK4

The full-length human PAK4 cDNA (SEQ ID NO:27) is 3604 bp long and consists of a 2043 bp ORF (143-2185) flanked by a 142 bp (1-142) 5'UTR and a 1419 3' UTR followed by a 22 nucleotide polydenylated region. A potential polyadenylation signal (AATTAAA) is found at positions 3582-3588. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human PAK4.

Multiple EST fragments (AA535791) match the 3'end of the human PAK4 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

Mammalian PAK5

The full-length human PAK5 cDNA (SEQ ID NO:102) is 2806 bp long and consists of a 1773 bp ORF flanked by a 201 bp 5' UTR and a 833 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (supra) for an initiating methionine, and is believed to be the translational start site for PAK5.

Multiple EST fragments (AA442867) match the 3'end of the human PAK5 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

II. Nucleic Acid Probes, Methods, and Kits for Detection of STE20-Related Kinases.

A nucleic acid probe of the present invention may be used to probe an appropriate chromosomal or cDNA library by usual hybridization methods to obtain other nucleic acid molecules of the present invention. A chromosomal DNA or cDNA library may be prepared from appropriate cells according to recognized methods in the art (cf. "Molecular Cloning: A Laboratory Manual", second edition, Cold Spring Harbor Laboratory, Sambrook, Fritsch, & Maniatis, eds., 1989).

In the alternative, chemical synthesis can be carried out in order to obtain nucleic acid probes having nucleotide sequences which correspond to N-terminal and C-terminal portions of the amino acid sequence of the polypeptide of interest. The synthesized nucleic acid probes may be used

as primers in a polymerase chain reaction (PCR) carried out in accordance with recognized PCR techniques, essentially according to PCR Protocols, "A Guide to Methods and Applications", Academic Press, Michael, *et al.*, eds., 1990, utilizing the appropriate chromosomal or cDNA library to obtain the fragment of the present invention.

One skilled in the art can readily design such probes based on the sequence disclosed herein using methods of computer alignment and sequence analysis known in the art ("Molecular Cloning: A Laboratory Manual", 1989, supra). The hybridization probes of the present invention can be labeled by standard labeling techniques such as with a radiolabel, enzyme label, fluorescent label, biotin-avidin label, chemiluminescence, and the like. After hybridization, the probes may be visualized using known methods.

The nucleic acid probes of the present invention include RNA, as well as DNA probes, such probes being generated using techniques known in the art. The nucleic acid probe may be immobilized on a solid support. Examples of such solid supports include, but are not limited to, plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, and acrylic resins, such as polyacrylamide and latex beads. Techniques for coupling nucleic acid probes to such solid supports are well known in the art.

The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are

well known in the art and can be readily adapted in order to obtain a sample which is compatible with the method utilized.

One method of detecting the presence of nucleic acids of the invention in a sample comprises (a) contacting said sample with the above-described nucleic acid probe under conditions such that hybridization occurs, and (b) detecting the presence of said probe bound to said nucleic acid molecule. One skilled in the art would select the nucleic acid probe according to techniques known in the art as described above. Samples to be tested include but should not be limited to RNA samples of human tissue.

A kit for detecting the presence of nucleic acids of the invention in a sample comprises at least one container means having disposed therein the above-described nucleic acid probe. The kit may further comprise other containers comprising one or more of the following: wash reagents and reagents capable of detecting the presence of bound nucleic acid probe. Examples of detection reagents include, but are not limited to radiolabelled probes, enzymatic labeled probes (horseradish peroxidase, alkaline phosphatase), and affinity labeled probes (biotin, avidin, or steptavidin).

In detail, a compartmentalized kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allow the efficient transfer of reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the probe or primers used in the

assay, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, and the like), and containers which contain the reagents used to detect the hybridized probe, bound antibody, amplified product, or the like. One skilled in the art will readily recognize that the nucleic acid probes described in the present invention can readily be incorporated into one of the established kit formats which are well known in the art.

III. DNA Constructs Comprising a STE20-Related Nucleic Acid Molecule and Cells Containing These Constructs.

The present invention also relates to a recombinant DNA molecule comprising, 5' to 3', a promoter effective to initiate transcription in a host cell and the above-described nucleic acid molecules. In addition, the present invention relates to a recombinant DNA molecule comprising a vector and an above-described nucleic acid molecule. The present invention also relates to a nucleic acid molecule comprising a transcriptional region functional in a cell, a sequence complementary to an RNA sequence encoding an amino acid sequence corresponding to the above-described polypeptide, and a transcriptional termination region functional in said cell. The above-described molecules may be isolated and/or purified DNA molecules.

The present invention also relates to a cell or organism that contains an above-described nucleic acid molecule and thereby is capable of expressing a polypeptide. The polypeptide may be purified from cells which have been altered to express the polypeptide. A cell is said to be "altered to express a desired polypeptide" when the cell, through genetic manipulation, is made to produce a protein which it normally does not produce or which the cell normally produces at lower levels. One skilled in the art

can readily adapt procedures for introducing and expressing either genomic, cDNA, or synthetic sequences into either eukaryotic or prokaryotic cells.

A nucleic acid molecule, such as DNA, is said to be "capable of expressing" a polypeptide if it contains nucleotide sequences which contain transcriptional and translational regulatory information and such sequences are "operably linked" to nucleotide sequences which encode the polypeptide. An operable linkage is a linkage in which the regulatory DNA sequences and the DNA sequence sought to be expressed are connected in such a way as to permit gene sequence expression. The precise nature of the regulatory regions needed for gene sequence expression may vary from organism to organism, but shall in general include a promoter region which, in prokaryotes, contains both the promoter (which directs the initiation of RNA transcription) as well as the DNA sequences which, when transcribed into RNA, will signal synthesis initiation. Such regions will normally include those 5'-non-coding sequences involved with initiation of transcription and translation, such as the TATA box, capping sequence, CAAT sequence, and the like.

If desired, the non-coding region 3' to the sequence encoding a kinase of the invention may be obtained by the above-described methods. This region may be retained for its transcriptional termination regulatory sequences, such as termination and polyadenylation. Thus, by retaining the 3'-region naturally contiguous to the DNA sequence encoding a kinase of the invention, the transcriptional termination signals may be provided. Where the transcriptional termination signals are not satisfactorily functional in the expression host cell, then a 3' region functional in the host cell may be substituted.

Two DNA sequences (such as a promoter region sequence and a sequence encoding a kinase of the invention) are said to be operably linked if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region sequence to direct the transcription of a gene sequence encoding a kinase of the invention, or (3) interfere with the ability of the gene sequence of a kinase of the invention to be transcribed by the promoter region sequence. Thus, a promoter region would be operably linked to a DNA sequence if the promoter were capable of effecting transcription of that DNA sequence. Thus, to express a gene encoding a kinase of the invention, transcriptional and translational signals recognized by an appropriate host are necessary.

The present invention encompasses the expression of a gene encoding a kinase of the invention (or a functional derivative thereof) in either prokaryotic or eukaryotic cells. Prokaryotic hosts are, generally, very efficient and convenient for the production of recombinant proteins and are, therefore, one type of preferred expression system for kinases of the invention. Prokaryotes most frequently are represented by various strains of *E. coli*. However, other microbial strains may also be used, including other bacterial strains.

In prokaryotic systems, plasmid vectors that contain replication sites and control sequences derived from a species compatible with the host may be used. Examples of suitable plasmid vectors may include pBR322, pUC118, pUC119 and the like; suitable phage or bacteriophage vectors may include γgt10, γgt11 and the like; and suitable virus vectors may include pMAM-neo, pKRC and the like. Preferably, the

selected vector of the present invention has the capacity to replicate in the selected host cell.

Recognized prokaryotic hosts include bacteria such as *E. coli, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia*, and the like. However, under such conditions, the polypeptide will not be glycosylated. The prokaryotic host must be compatible with the replicon and control sequences in the expression plasmid.

To express a kinase of the invention (or a functional derivative thereof) in a prokaryotic cell, it is necessary to operably link the sequence encoding the kinase of the invention to a functional prokaryotic promoter. Such promoters may be either constitutive or, more preferably, regulatable (*i.e.*, inducible or derepressible). Examples of constitutive promoters include the *int* promoter of bacteriophage λ, the *bla* promoter of the β-lactamase gene sequence of pBR322, and the *cat* promoter of the chloramphenicol acetyl transferase gene sequence of pPR325, and the like. Examples of inducible prokaryotic promoters include the major right and left promoters of bacteriophage λ (P_L and P_R), the *trp, recA, λacZ, λacI*, and *gal* promoters of *E. coli*, the α-amylase (Ulmanen *et al.*, J. Bacteriol. 162:176-182, 1985) and the ς-28-specific promoters of *B. subtilis* (Gilman *et al.*, Gene Sequence 32:11-20, 1984), the promoters of the bacteriophages of *Bacillus* (Gryczan, In: The Molecular Biology of the Bacilli, Academic Press, Inc., NY, 1982), and *Streptomyces* promoters (Ward *et al.*, Mol. Gen. Genet. 203:468-478, 1986). Prokaryotic promoters are reviewed by Glick (Ind. Microbiot. 1:277-282, 1987), Cenatiempo (Biochimie 68:505-516, 1986), and Gottesman (Ann. Rev. Genet. 18:415-442, 1984).

Proper expression in a prokaryotic cell also requires the presence of a ribosome-binding site upstream of the gene

sequence-encoding sequence. Such ribosome-binding sites are disclosed, for example, by Gold *et al.* (Ann. Rev. Microbiol. 35:365-404, 1981). The selection of control sequences, expression vectors, transformation methods, and the like, are dependent on the type of host cell used to express the gene. As used herein, "cell", "cell line", and "cell culture" may be used interchangeably and all such designations include progeny. Thus, the words "transformants" or "transformed cells" include the primary subject cell and cultures derived therefrom, without regard to the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. However, as defined, mutant progeny have the same functionality as that of the originally transformed cell.

Host cells which may be used in the expression systems of the present invention are not strictly limited, provided that they are suitable for use in the expression of the kinase polypeptide of interest. Suitable hosts may often include eukaryotic cells. Preferred eukaryotic hosts include, for example, yeast, fungi, insect cells, mammalian cells either *in vivo*, or in tissue culture. Mammalian cells which may be useful as hosts include HeLa cells, cells of fibroblast origin such as VERO or CHO-K1, or cells of lymphoid origin and their derivatives. Preferred mammalian host cells include SP2/0 and J558L, as well as neuroblastoma cell lines such as IMR 332, which may provide better capacities for correct post-translational processing.

In addition, plant cells are also available as hosts, and control sequences compatible with plant cells are available, such as the cauliflower mosaic virus 35S and 19S, and nopaline synthase promoter and polyadenylation signal sequences. Another preferred host is an insect cell, for

example the *Drosophila* larvae. Using insect cells as hosts, the *Drosophila* alcohol dehydrogenase promoter can be used (Rubin, Science 240:1453-1459, 1988). Alternatively, baculovirus vectors can be engineered to express large amounts of kinases of the invention in insect cells (Jasny, Science 238:1653, 1987; Miller *et al.*, In: Genetic Engineering, Vol. 8, Plenum, Setlow *et al.*, eds., pp. 277-297, 1986).

Any of a series of yeast expression systems can be utilized which incorporate promoter and termination elements from the actively expressed sequences coding for glycolytic enzymes that are produced in large quantities when yeast are grown in mediums rich in glucose. Known glycolytic gene sequences can also provide very efficient transcriptional control signals. Yeast provides substantial advantages in that it can also carry out post-translational modifications. A number of recombinant DNA strategies exist utilizing strong promoter sequences and high copy number plasmids which can be utilized for production of the desired proteins in yeast. Yeast recognizes leader sequences on cloned mammalian genes and secretes peptides bearing leader sequences (*i.e.*, pre-peptides). Several possible vector systems are available for the expression of kinases of the invention in a mammalian host.

A wide variety of transcriptional and translational regulatory sequences may be employed, depending upon the nature of the host. The transcriptional and translational regulatory signals may be derived from viral sources, such as adenovirus, bovine papilloma virus, cytomegalovirus, simian virus, or the like, where the regulatory signals are associated with a particular gene sequence which has a high level of expression. Alternatively, promoters from mammalian expression products, such as actin, collagen,

myosin, and the like, may be employed. Transcriptional initiation regulatory signals may be selected which allow for repression or activation, so that expression of the gene sequences can be modulated. Of interest are regulatory signals which are temperature-sensitive so that by varying the temperature, expression can be repressed or initiated, or are subject to chemical (such as metabolite) regulation.

Expression of kinases of the invention in eukaryotic hosts requires the use of eukaryotic regulatory regions. Such regions will, in general, include a promoter region sufficient to direct the initiation of RNA synthesis. Preferred eukaryotic promoters include, for example, the promoter of the mouse metallothionein I gene sequence (Hamer *et al.*, J. Mol. Appl. Gen. 1:273-288, 1982); the TK promoter of Herpes virus (McKnight, Cell 31:355-365, 1982); the SV40 early promoter (Benoist *et al.*, Nature (London) 290:304-31, 1981); and the yeast gal4 gene sequence promoter (Johnston *et al.*, Proc. Natl. Acad. Sci. (USA) 79:6971-6975, 1982; Silver *et al.*, Proc. Natl. Acad. Sci. (USA) 81:5951-5955, 1984).

Translation of eukaryotic mRNA is initiated at the codon which encodes the first methionine. For this reason, it is preferable to ensure that the linkage between a eukaryotic promoter and a DNA sequence which encodes a kinase of the invention (or a functional derivative thereof) does not contain any intervening codons which are capable of encoding a methionine (*i.e.*, AUG). The presence of such codons results either in the formation of a fusion protein (if the AUG codon is in the same reading frame as the kinase of the invention coding sequence) or a frame-shift mutation (if the AUG codon is not in the same reading frame as the kinase of the invention coding sequence).

A nucleic acid molecule encoding a kinase of the invention and an operably linked promoter may be introduced into a recipient prokaryotic or eukaryotic cell either as a nonreplicating DNA or RNA molecule, which may either be a linear molecule or, more preferably, a closed covalent circular molecule. Since such molecules are incapable of autonomous replication, the expression of the gene may occur through the transient expression of the introduced sequence. Alternatively, permanent expression may occur through the integration of the introduced DNA sequence into the host chromosome.

A vector may be employed which is capable of integrating the desired gene sequences into the host cell chromosome. Cells which have stably integrated the introduced DNA into their chromosomes can be selected by also introducing one or more markers which allow for selection of host cells which contain the expression vector. The marker may provide for prototrophy to an auxotrophic host, biocide resistance, *e.g.*, antibiotics, or heavy metals, such as copper, or the like. The selectable marker gene sequence can either be directly linked to the DNA gene sequences to be expressed,, or introduced into the same cell by co-transfection. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include splice signals, as well as transcription promoters, enhancers, and termination signals. cDNA expression vectors incorporating such elements include those described by Okayama (Mol. Cell. Biol. 3:280-, 1983).

The introduced nucleic acid molecule can be incorporated into a plasmid or viral vector capable of autonomous replication in the recipient host. Any of a wide variety of vectors may be employed for this purpose. Factors of importance in selecting a particular plasmid or

viral vector include: the ease with which recipient cells that contain the vector may be recognized and selected from those recipient cells which do not contain the vector; the number of copies of the vector which are desired in a particular host; and whether it is desirable to be able to "shuttle" the vector between host cells of different species.

Preferred prokaryotic vectors include plasmids such as those capable of replication in *E. coli* (such as, for example, pBR322, ColE1, pSC101, pACYC 184, πVX; "Molecular Cloning: A Laboratory Manual", 1989, supra). Bacillus plasmids include pC194, pC221, pT127, and the like (Gryczan, In: The Molecular Biology of the Bacilli, Academic Press, NY, pp. 307-329, 1982). Suitable *Streptomyces* plasmids include p1J101 (Kendall *et al.*, J. Bacteriol. 169:4177-4183, 1987), and streptomyces bacteriophages such as φC31 (Chater *et al.*, In: Sixth International Symposium on Actinomycetales Biology, Akademiai Kaido, Budapest, Hungary, pp. 45-54, 1986). *Pseudomonas* plasmids are reviewed by John *et al.* (Rev. Infect. Dis. 8:693-704, 1986), and Izaki (Jpn. J. Bacteriol. 33:729-742, 1978).

Preferred eukaryotic plasmids include, for example, BPV, vaccinia, SV40, 2-micron circle, and the like, or their derivatives. Such plasmids are well known in the art (Botstein *et al.*, Miami Wntr. Symp. 19:265-274, 1982; Broach, In: "The Molecular Biology of the Yeast Saccharomyces: Life Cycle and Inheritance", Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p. 445-470, 1981; Broach, Cell 28:203-204, 1982; Bollon *et al.*, J. Clin. Hematol. Oncol. 10:39-48, 1980; Maniatis, In: Cell Biology: A Comprehensive Treatise, Vol. 3, Gene Sequence Expression, Academic Press, NY, pp. 563-608, 1980).

Once the vector or nucleic acid molecule containing the construct(s) has been prepared for expression, the DNA construct(s) may be introduced into an appropriate host cell by any of a variety of suitable means, *i.e.*, transformation, transfection, conjugation, protoplast fusion, electroporation, particle gun technology, calcium phosphate-precipitation, direct microinjection, and the like. After the introduction of the vector, recipient cells are grown in a selective medium, which selects for the growth of vector-containing cells. Expression of the cloned gene(s) results in the production of a kinase of the invention, or fragments thereof. This can take place in the transformed cells as such, or following the induction of these cells to differentiate (for example, by administration of bromodeoxyuracil to neuroblastoma cells or the like). A variety of incubation conditions can be used to form the peptide of the present invention. The most preferred conditions are those which mimic physiological conditions.

IV. The Proteins of the Invention

A variety of methodologies known in the art can be utilized to obtain the polypeptides of the present invention. The polypeptides may be purified from tissues or cells that naturally produce the polypeptides. Alternatively, the above-described isolated nucleic acid fragments could be used to express the kinases of the invention in any organism. The samples of the present invention include cells, protein extracts or membrane extracts of cells, or biological fluids. The samples will vary based on the assay format, the detection method, and the nature of the tissues, cells or extracts used as the sample.

Any eukaryotic organism can be used as a source for the polypeptides of the invention, as long as the source organism naturally contains such polypeptides. As used herein, "source organism" refers to the original organism from which the amino acid sequence of the subunit is derived, regardless of the organism the subunit is expressed in and ultimately isolated from.

One skilled in the art can readily follow known methods for isolating proteins in order to obtain the polypeptides free of natural contaminants. These include, but are not limited to: size-exclusion chromatography, HPLC, ion-exchange chromatography, and immuno-affinity chromatography.

Mammalian STLK2

Analysis of the deduced amino acid sequence predicts STLK2 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. STLK2 contains a 21 amino acid N-terminal domain, a 253 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, followed by a 142 amino acid C-terminal domain.

STLK2 is most closely related to human STE20-subfamily kinases, MST3 (GB:AF024636) and SOK-1 (GB:X99325) and a *C. elegans* kinase yk34b11.5 (GB:U53153) sharing 72.7%, 68.7%, and 69.3% amino acid identity, respectively.

The 21 amino acid N-terminal domain of human STLK2 is 71.4% identical to the N-terminus of MST3 (GB:AF024636). Human STLK2 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation. A Smith-Waterman search of the nonredundant protein database does not reveal any significant homologies that might suggest a potential function for this domain.

The 253 amino acid catalytic domain of human STLK2 is most related to human SOK-1 (X99325), MST3 (GB:AF024636), *C. elegans* yk32b11.5 (GB:U53153), and STLK3 (SEQ ID NO:6) sharing 88.9%, 87.4%, 78.3%, and 49% amino identity respectively, placing it in the STLK-subfamily of STE20-related kinases. The STLK2 kinase domain displayed lesser homology to other STE20-related kinases including: 55.9% to human MST2 (GB:U26424), 49.2% to human GCK (GB:U07349), 49.2% to human KHS1 (GB:U77129), and 44.2% to human HPK1 (GB:U66464). The activation loop of human STLK2 catalytic domain is identical to that of human SOK-1 and MST3 including the presence of four potential threonine phosphorylation sites that could serve an autoregulatory role on kinase activity.

The 142 amino acid C-terminal domain of human STLK2 is most related to human SOK-1 (X99325), MST3 (GB:AF024636), and *C. elegans* yk32b11.5 (GB:U53153), sharing 39.9%, 39.9%, and 33.3% amino acid identity, respectively. This C-terminal domain shares some significant amino acid similarity to the C-terminal domains of the related human STLK3 (SEQ ID NO:6) and STLK4 (SEQ ID NO:7).

The C-terminus of the related human SOK-1 (GB:X99325) kinase has been shown to be inhibitory to the catalytic activity of this kinase (Pombo, C.M., Bonventre, J.V., Molnar, A., Kyriakis, J. and Force, T. EMBO J. 15, 4537-4546 (1996)). Based on the sequence identity between the C-termini of human SOK-1 (GB:X99325) and human STLK2 (39.2%), the C-terminus of human STLK2 may also function as an inhibitory domain for its kinase.

<u>Mammalian STLK3</u>

The 3030 bp human STLK3 nucleotide sequence of the partial cDNA clone encodes a polypeptide of 516 amino acids

(SEQ ID NO:6) with a predicted molecular mass of 56,784 daltons. Analysis of the deduced amino acid sequence predicts STLK3 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain, however the cDNA clone lacks an initiating ATG, so the full extent of it N-termius is not known. STLK3 contains a 31 amino acid N-terminal domain, a 277 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, followed by a 181 amino acid C-terminal domain containing a 25 amino acid insert and a 27 amino acid tail relative to the sequence of human STLK2.

STLK3 is most closely related to human STE20-subfamily kinases, STLK4 (SEQ ID. NO:7), MST3 (GB:AF024636), SOK-1 (GB:X99325) and STLK2 (SEQ ID NO:5) sharing 71.1%, 37.6%, 38.1%, and 38.4% amino acid identity respectively.

The 31 amino acid N-terminal domain of human STLK3 lacked any significant amino acid sequence homologies using a Smith-Waterman search of the nonredundant protein database, other than sequence similarity to proline-alanine repeats.

The 277 amino acid catalytic domain of human STLK3 is most related to human STLK4 (SEQ ID NO:7), SOK-1 (GB:X99325), MST3 (GB:AF024636), and STLK2 (SEQ ID NO:5) sharing 88.2%, 49.2%, 49%, and 49% amino acid identity, respectively. It also shares strong homology to other STKs from lower organisms including 51.7% to *A. thaliana* (GB: AC002343), 43.1% to *A. thaliana* (GB: Z97336), 42.1% to *A. thaliana* (GB: U96613), and 43.3% to *C. elegans* (GB: U53153). The activation loop of the human STLK3 catalytic domain conserves three potential threonine phosphorylation sites with other members of the STLK-subfamily of STE20-related kinases (human STE20, MST3, STLK2, STLK4) that could serve an autoregulatory role on kinase activity.

The 181 amino acid C-terminal domain of human STLK3 shares 55.5% amino acid identity to human STLK4 (SEQ ID NO:7), and is 100% identical to a partial human cDNA DCHT (GB:AF017635). The C-terminal domain of human STLK3 contains a 26 amino acid insert relative to human STE20. A similar (87.5% amino acid identity) 26 amino acid insert is also present in human STLK4.

The 27 amino acid C-terminal tail of human STLK3 shares 77.8% amino acid identity to human STLK4, but is absent from other STLK-family members. This high degree of homology between the C-tail of two STLK-family members suggests they may be involved in an as yet unidentified protein-protein interaction.

The weak sequence homology between the C-termini of human STLK3 and STE20, suggests it may also function as an inhibitory domain for its kinase.

<u>Mammalian STLK4</u>

The 3857 bp human STLK4 nucleotide sequence of the partial cDNA clone encodes a polypeptide of 414 amino acids (SEQ ID NO:7) with a predicted molecular mass of 45,451 daltons. Analysis of the deduced amino acid sequence predicts STLK4 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain, however the cDNA clone lacks an initiating ATG, so the full extent of it N-terminus is not known. The partial STLK4 protein sequence contains a 178 amino acid catalytic domain corresponding to the C-terminal motifs VI-XI of a serine/threonine kinase, followed by a 236 amino acid C-terminal domain containing two inserts of 25 and 41 amino acids each, relative to the sequence of human STLK2.

STLK4 is most closely related to human STE20-subfamily kinases, STLK3 (SEQ ID. NO 6), MST3 (GB:AF024636), STLK2

(SEQ ID NO:5), and SOK-1 (GB:X99325) sharing 71.0%, 46.8%, 43.9%, and 37.7% amino acid identity, respectively.

The 178 amino acid catalytic domain of human STLK4 is most related to human STLK3 (SEQ ID NO. 7), SOK-1 (GB:X99325), MST3 (GB:AF024636), STLK2 (SEQ ID NO:5), and MST1 (GB:U18297), sharing 88.2%, 54.2%, 54.0%, 53.7 and 45.7% amino acid identity, respectively. It also shares strong homology to other STKs from lower organisms including 56.9% to *A. thaliana* (GB: AC002343), 52.5% to *C. elegans* (GB: U53153), 46.2% to *A. thaliana* (GB: Z97336) and 45.7% to *A. thaliana* (GB: U96613). The activation loop of the human STLK4 catalytic domain conserves three potential threonine phosphorylation sites with other members of the STLK-subfamily of STE20-related kinases (human STE20, MST3, STLK2 and STLK3) that could serve an autoregulatory role on kinase activity.

The 236 amino acid C-terminal domain of human STLK4 shares 58.1% amino acid identity to both human STLK3 (SEQ ID NO:6) and to a partial human cDNA, DCHT (GB:AF017635). The C-terminal domain of human STLK4 contains a 25 amino acid insert relative to human SOK-1 and shares 87.5% amino acid identity to an insert present in human STLK3.

The weak sequence homology between the C-termini of human STLK4 and STE20, suggests it may also function as an inhibitory domain for its kinase.

<u>Mammalian STLK5</u>

The full-length 2110 bp human STLK5 cDNA encodes a polypeptide of 373 amino acids (SEQ ID NO:97) with a predicted molecular mass of 41,700 daltons. Analysis of the deduced amino acid sequence predicts STLK5 to be an intracellular STE20-subfamily kinase, lacking both a signal sequence and transmembrane domain. STLK5 contains a 10

amino acid N-terminal domain, a 311 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, and a 52 amino acid C-terminal domain.

STLK5 is most closely related to the human STE20-subfamily kinases STLK6 (SEQ ID No. 99) and SPAK (AF099989), sharing 51% and 33% amino acid identity, respectively, over its full extent. It also shares significant homology to database entries from *Arabidopsis thaliana* (GB:AC002343) and *C.elegans* (GB:AL023843, GB:AL023843).

The 10 amino acid N-terminal domain of human STLK5 does not reveal any significant homologies to the protein database.

The 311 amino acid catalytic domain of human STLK5 shares 51% and 34 % identity to STLK6 and SPAK, respectively. The catalytic domain of STLK5 contains a 45 amino acid insert between kinase subdomains X and XI relative to human STE20. Multiple human EST fragments as well as a murine EST (GB:AA575647) contain this insert providing evidence that this region is an integral part of STLK5.

The 52 amino acid C-terminal tail of human STLK5 shares 41.3% amino acid identity to human SOK-1 (GB:X99325). The weak sequence homology between the C-termini of human STLK5 and STE20, suggests it may also function as an inhibitory domain for its kinase.

Mammalian STLK6

The 2,001 bp human STLK6 nucleotide sequence of the complete cDNA encodes a polypeptide of 418 amino acids (SEQ ID NO:99) with a predicted molecular mass of 47,025 daltons. Analysis of the deduced amino acid sequence predicts STLK6 to be an intracellular STE20-subfamily kinase, lacking both

a signal sequence and transmembrane domain. STLK6 contains a 57 amino acid N-terminal domain, a 312 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, followed by a 49 amino acid C-terminal domain.

STLK6 is most closely related to human STE20-subfamily kinases STLK5 (SEQ ID NO:97), STLK7 (SEQ ID NO:101), and SPAK (AFO99989), sharing 50%, 35%, and 30% amino acid identity over its full extent. It also shares significant homology to database entries from *Arabidopsis thaliana* (GB:AC002343) and *C.elegans* (GB:U53153).

The 57 amino acid N-terminal domain of human STLK6 does not reveal any significant homologies in the protein database.

The 312 amino acid catalytic domain of human STLK6 shares 51 and 30 % identity to human STLK5 and SPAK, respectively.

The 49 amino acid C-terminal tail of human STLK6 shares low amino acid sequence identity (29%) with STLK5 and SPAK.

Mammalian STLK7

The 311 bp human STLK7 nucleotide sequence of the partial cDNA encodes a polypeptide of 103 amino acids (SEQ ID NO:101). Analysis of the deduced amino acid sequence predicts STLK7 to be an internal fragment of an intracellular STE20-family kinase. This sequence lacks the N- and C-terminal portions of STLK7 and contains only the N-terminal 103 amino acids of the predicted catalytic domain.

Human STLK7 is most closely related to human STE20-subfamily kinases SPAK (AFO99989), STLK5 (SEQ ID NO:97), and STLK6 (SEQ ID NO:99), sharing 86%, 38%, and 35% amino acid identity within this region of the kinase domain. It also

shares significant homology to database entries from *Arabidopsis thaliana* (GB:AC002343) and *Drosophila melanogaster* (GB:AF006640).

Mammalian ZC1

The 3798 bp human ZC1 nucleotide sequence encodes a polypeptide of 1239 amino acids (SEQ ID NO:13) with a predicted molecular mass of 142,140 daltons. Analysis of the deduced amino acid sequence predicts ZC1 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The full-length ZC1 protein contains a 22 amino acid N-terminus, a 267 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 237 amino acid region predicted to form a coiled-coil structure, a 114 amino acid proline-rich region, a 256 amino acid spacer region, followed by a 343 amino acid C-terminal domain containing a potential Rab/Rho-binding region.

ZC1 is most closely related to the human STE20-subfamily kinases ZC2 (SEQ ID NO:14), ZC3 (SEQ ID NO:15), and ZC4 (SEQ ID NO:16), sharing 61.7%, 60.9%, and 43.8% amino acid identity, respectively. ZC1 also shares 45.5% amino acid identity to a *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029). ZC1 exhibits 90.0% amino acid homology to murine NIK (GB:U88984), suggesting it may be the human orthologue of this STK.

The 22 amino acid N-terminal domain of human ZC1 is 58.8% identical to the *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029), and 100% identical to murine NIK (GB: U88984). Human ZC1 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation. A Smith-Waterman search of the nonredundant protein database

does not reveal any significant homologies that might suggest a potential function for this domain.

The 267 amino acid catalytic domain of human ZC1 is most related to human STE20-subfamily kinases, ZC3 (SEQ ID NO:15), ZC2 (SEQ ID NO:14), KHS2 (SEQ ID NO:18), SOK-1 (GB:X99325), GCK (GB:U07349), and GEK2 (SEQ ID NO:107), and to the *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029) sharing 90.6%, 90.2%, 50.6%, 47.4%, 45.4%, 42.5% and 82.6% amino acid identity, respectively. The ZC1 kinase domain shares 98.1% identity to murine NIK (GB:U88984). ZC1 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

Immediately C-terminal to the kinase domain of human ZC1 is a 237 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (Lupas, A. Meth. Enzymol. 266, 513-525 (1996)). This region of ZC1 is most related to human STE20-subfamily kinases, ZC3 (SEQ ID NO:15), ZC2 (SEQ ID NO:14), and GEK2 (SEQ ID NO:107), as well as to human PITSLRE (GB:U04824) sharing 65.5%, 65.4%, 25.3%, and 29.0% amino acid identity, respectively. The ZC1 coiled-coil domain also shares 90.6% amino acid homology to murine NIK. The *C. elegans* homologue ZC504.4 shares 32.2% sequence identity over this region.

Within the predicted coiled-coil domain of human ZC1, and the related ZC3, is a region predicted to form a leucine zipper (Leu-X6-Leu-X6-Leu-X6-Leu-X20-Leu-X6-Leu). The fact that this leucine repeat exists within a predicted coiled-coil structure suggests that the leucine zipper may have a high probability of serving as a dimerization interface (Hirst, J.D. *et al* Protein Engineering 9 657-662 (1996))

mediating a potential inter- or intra-molecular dimerization of human ZC1.

The 114 amino acid proline-rich region of human ZC1 is most related to human STE20-subfamily kinases, ZC2 (SEQ ID NO:14) and ZC3 (SEQ ID NO:15), sharing 35.8%, and 24.9%, respectively. The ZC1 proline-rich domain shares 36.4% amino acid homology to murine NIK (GB:U88984). Three potential "PxxP" SH3 domain-binding motifs (I, II and III) are found within the proline-rich region of human ZC1. Motif I is conserved in human ZC1 and *C. elegans* ZC504.4 (GB:Z50029). Motif II is conserved in ZC1, ZC2, ZC3, ZC4 and *C. elegans* ZC504.4. Motif III is conserved in ZC1, ZC2, ZC3 and ZC4. Motifs II and III of murine NIK have been shown to bind the SH3 motif of the adaptor molecule Nck (Su, Y-C. *et al*, EMBO J. 16, 1279-1290 (1997)). From this evidence, human ZC1 may have the potential to bind to Nck or other SH3 or WW domain-containing proteins and participate in growth factor-induced signaling pathways.

The 256 amino acid spacer region of human ZC1 is most related to human STE20-subfamily kinases, ZC2 (SEQ ID NO:14) and ZC3 (SEQ ID NO:15), as well as to human PITSLRE (GB:U04824), sharing 59.9%, 33.1%, 29.6%, and 26.4% amino acid identity, respectively. It also shares 59.9% amino acid homology to murine NIK. The *C. elegans* homologue ZC504.4 has only limited sequence similarity in this spacer region.

The 343 amino acid C-terminal of human ZC1 is most related to human STE20-subfamily kinases, ZC3 (SEQ ID NO:15), ZC2 (SEQ ID NO:14), and ZC4 (SEQ ID NO:16), sharing 89.2%, 88.9%, and 42.3%, amino acid identity, respectively. The ZC1 C-terminal domain also shares 98.8% amino acid identity to murine NIK. The *C. elegans* homologue ZC504.4 also shares 68.7% amino acid identity with the C-tail of

human ZC1. A lower, yet significant, homology is also evident to human KHS2 (SEQ ID NO:18), GCK (GB:U07349), and murine citron (GB:U07349) with 26.6%, 23.1% and 36.2% amino acid identity, respectively. GCK is a STE20-family kinase whose C-terminal domain has been shown to bind the small G-protein Rab8 (Ren, M. *et al.*, Proc. Natl. Acad. Sci. 93, 5151-5155 (1996)). Citron is a non-kinase Rho-binding protein (Madaule, P. *et al.*, FEBS Lett. 377, 243-238 (1995)).

The sequence similarity of the C-terminal region of ZC1 to proteins that have potential Rab- or Rho-binding domains suggests that ZC1 may signal through a small G-protein-dependant pathway.

Mammalian ZC2

The 4055 bp human ZC2 nucleotide sequence of the partial cDNA encodes a polypeptide of 1297 amino acids (SEQ ID NO:14) with a predicted molecular mass of 147,785 daltons. Analysis of the deduced amino acid sequence predicts ZC2 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain, however the cDNA clone lacks an initiating ATG, so the full extent of it N-terminus is not known. The N-terminally truncated ZC2 protein contains a 255 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 187 amino acid region predicted to form a coiled-coil structure, a 184 amino acid proline-rich region, a 328 amino acid spacer region, followed by a 343 amino acid C-terminal domain containing a potential Rab/Rho-binding region.

ZC2 is most closely related to the human STE20-subfamily kinases ZC3 (SEQ ID NO:15), ZC1 (SEQ ID NO:13), and ZC4 (SEQ ID NO:16), sharing 88.3%, 61.7%, and 41.9%

amino acid identity, respectively, and shares 41.7% amino acid identity to a *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029).

The 255 amino acid catalytic domain of human ZC2 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), SOK-1 (GB:X99325), KHS2 (SEQ ID NO:18), MST1 (GB:U18297), and GCK (GB:U07349), and to the *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029) sharing 90.2%, 89.8%, 49.0%, 48.6%, 47.9%, 45.0 and 76.7% amino acid identity, respectively. ZC2 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

Immediately C-terminal to the kinase domain of human ZC2 is a 187 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (supra). This region of ZC2 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), and GEK2 (SEQ ID NO:107), as well as to human PITSLRE (GB:U04824), sharing 65.8%, 61.5%, 29.7% and 29.6% amino acid identity, respectively. The *C. elegans* homologue ZC504.4 shares 30.8% sequence identity over this region. Human ZC2 lacks the potential leucine zipper found in ZC1 as a consequence of a 29 amino acid deletion relative to ZC1 and ZC3.

The 184 amino acid proline-rich region of human ZC2 is most related to human STE20-subfamily kinases, ZC3 (SEQ ID NO:15) and ZC1 (SEQ ID NO:13), sharing 35.9% and 28.6%,amino acid identity, respectively. Significant homology is also evident to the murine WW domain-binding protein WBP7 (GB:U92455), and to the human SH3 domain-binding protein 3BP-1 (GB:X87671), with 27.7% and 25.3% amino acid identity, respectively.

ZC2 contains two of the potential "PxxP" SH3 domain-binding motifs (II and III) found within the proline-rich region of human ZC1. Motif II is conserved in ZC1, ZC3, ZC4 and *C. elegans* ZC504.4, and Motif III is conserved in ZC1, ZC3 and ZC4. Motifs II and III of murine NIK have been shown to bind the SH3 motif of the adaptor molecule Nck. From this evidence, human ZC1 may have the potential to bind to Nck or other SH3 or WW domain-containing proteins, and to participate in growth factor-induced signaling pathways.

The 328 amino acid spacer region of human ZC2 is most related to human STE20-subfamily kinases ZC1 (SEQ ID NO:13) and ZC3 (SEQ ID NO:15), and to murine NIK (GB:U88984), sharing 31.6%, 26.9% and 25.9% amino acid identity, respectively. The *C. elegans* homologue ZC504.4 has only limited sequence similarity in this spacer region.

The 343 amino acid C-terminal of human ZC2 is most related to human STE20-subfamily kinases ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15) and ZC4 (SEQ ID NO:16), and to murine NIK (GB:U88984), sharing 88.9%, 88.3%, 41.9%, and 88.0%, amino acid identity, respectively. The *C. elegans* homologue, ZC504.4, also shares 67.2% amino acid identity with the C-tail of human ZC2. A lower, yet significant, homology is also evident to human GCK (GB:U07349), murine citron (GB:U07349), and the *S. cerevisiae* ROM2 protein (GB:U19103), a Rho1 GDP/GTP exchange factor, with 22.3%, 22.2% and 21.9% amino acid identity, respectively.

The sequence similarity of the C-terminal region of ZC2 to proteins that have potential Rab- or Rho-binding domains suggests that ZC2, like ZC1, may also signal through a small G-protein-dependant pathway.

Mammalian ZC3

The 4133 bp human ZC3 nucleotide sequence of the partial cDNA encodes a polypeptide of 1326 amino acids (SEQ ID NO:15) with a predicted molecular mass of 149,906 daltons. Analysis of the deduced amino acid sequence predicts ZC3 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain, however the cDNA clone lacks an initiating ATG, so the full extent of it N-termius is not known. The N-terminally truncated ZC3 protein contains a 255 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase: a 221 amino acid region predicted to form a coiled-coil structure, a 204 amino acid proline-rich region, and a 303 amino acid spacer region followed by a 343 amino acid C-terminal domain containing a potential Rab/Rho-binding region.

ZC3 is most closely related to the human STE20-subfamily kinases ZC1 (SEQ ID NO:13), ZC2 (SEQ ID NO:14), and ZC4 (SEQ ID NO:16), sharing 62.0%, 61.0%, and 42.5% amino acid identity, respectively and shares 46.7% amino acid identity to a *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029).

The 255 amino acid catalytic domain of human ZC3 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC2 (SEQ ID NO:14), SOK-1 (GB:X99325), KHS2 (SEQ ID NO:18), GCK (GB:U07349), SULU1 (SEQ ID NO:22), and GEK2 (SEQ ID NO:107), and to the *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029) sharing 90.6%, 89.3%, 49.0%, 48.3%, 45.0%, 43.1%, 42.3% and 76.7% amino acid identity, respectively. ZC1 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

Immediately C-terminal to the kinase domain of human ZC3 is a 221 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (supra). This region of ZC3 is most homologous to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC2 (SEQ ID NO:14), and GEK2 (SEQ ID NO:107), sharing 66.9%, 61.5%, and 27.5% identity, as well as to rat PLC-beta (GB:A45493) and human PITSLRE (GB:H54024) sharing 29.6% and 25.9% amino acid identity, respectively. The *C. elegans* homologue ZC504.4 shares 26.8% sequence identity over this region.

Within the predicted coiled-coil domain of human ZC3, and the related ZC1, is a region predicted to form a leucine zipper (Leu-X6-Leu-X6-Leu-X6-Leu-X20-Leu-X6-Leu). The fact that this leucine repeat exists within a predicted coiled-coil structure suggests that the leucine zipper may have a high probability of serving as a dimerization interface (Hirst, J.D. *et al* Protein Engineering 9 657-662 (1996)) mediating a potential inter- or intra-molecular dimerization of human ZC3.

The 204 amino acid proline-rich region of human ZC3 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13) and ZC2 (SEQ ID NO:14), sharing 66.9% and 61.5% amino acid identity, respectively.

ZC3 contains two of the potential "PxxP" SH3 domain-binding motifs (II and III) found within the proline-rich region of human ZC1. Motif II is conserved in ZC1, ZC2, ZC4 and *C. elegans* ZC504.4; Motif III is conserved in ZC1, ZC2 and ZC4. Motifs II and III of murine NIK have been shown to bind the SH3 motif of the adaptor molecule Nck. From this evidence, human ZC3 may have the potential to bind to Nck or other SH3 or WW domain-containing proteins and participate in growth factor-induced signaling pathways.

The 303 amino acid acid spacer region of human ZC3 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13) and ZC2 (SEQ ID NO:14) sharing 30.1%, and 27.1% amino acid identity, respectively. The *C. elegans* homologue ZC504.4 lacks nearly the entire spacer region of ZC3.

The 343 amino acid C-terminal of human ZC3 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC2 (SEQ ID NO:14) and ZC4 (SEQ ID NO:16), sharing 89.2%, 88.9%, and 42.5%, amino acid identity, respectively. The *C. elegans* homologue ZC504.4 also shares 67.2% amino acid identity with the C-tail of human ZC3. A lower, yet significant, homology is also evident to human GCK (GB:U07349), as well as to the non-kinases murine citron (GB:U07349) and the *S. cerevisiae* ROM2 protein (GB:U19103), a Rho1 GDP/GTP exchange factor, with 21.6%, 32.4% and 22.9% amino acid identity, respectively.

The sequence similarity of the C-terminal region of ZC3 to proteins that have potential Rab- or Rho-binding domains suggests that ZC3, like ZC1 and ZC2, may signal through a small G-protein-dependant pathway.

<u>Mammalian ZC4</u>

The 3,684 bp human ZC4 nucleotide sequence of the complete cDNA encodes a polypeptide of 1,227 amino acids (SEQ ID NO:105) with a predicted molecular mass of 138,205 Daltons. Analysis of the deduced amino acid sequence predicts ZC4 to be an intracellular STE20-subfamily kinase, lacking both a signal sequence and a transmembrane domain. The full-length ZC4 protein contains a 25 amino acid N-terminus, a 265 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 108 amino acid region predicted to form a coiled-coil structure, a 231 amino acid proline-rich region, a 40 amino acid region

predicted to form a coiled-coil structure spacer region, a 204 amino acid spacer region (domain B), followed by a 355 amino acid C-terminal domain containing a potential Rab/Rho-binding region (domain C).

ZC4 is most closely related to human ZC1 (SEQ ID NO:13, also known as human HGK, human KIAA0687, murine NIK, human AC005035, human NIK, and *C. elegans* MIG-15), ZC2 (SEQ ID NO:14, similar to partial sequence human KIAA0551), and ZC3 (SEQ ID NO:15). An assembled genomic fragment in the database (Z83850) is identical to ZC4, except for inappropriate identification of the exon boundaries. (Abo *et al*. (1998) EMBO J. 17: 6527-6540.)

The 25 amino acid N-terminal domain of human ZC4 shares weak homology to human ZC1 in its C-terminal extent, but otherwise does not reveal any significant homologies to the protein database.

The 265 amino acid catalytic domain of human ZC4 is most related to human ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), and ZC2 (SEQ ID NO:14), sharing 63%, 64% and 62% amino acid identity, respectively.

Immediately C-terminal to the kinase domain of human ZC4 is a 108 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (supra). This region is most related to human ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), and ZC2 (SEQ ID NO:14), sharing 29%, 25% and 20% amino acid identity, respectively.

The 231 amino acid proline-rich region of human ZC4 does not reveal any significant homologies to the protein database. This region of ZC4 contains two "PxxP" motifs that could potentially bind to proteins containing SH3 or WW domains and allow ZC4 to participate in growth factor activated signaling pathways. In addition, within the pro-rich domain of human ZC4 is a region predicted to form a

leucine zipper (Leu-X6-Leu-X6-Leu-X6-Leu-X20-Leu-X6-Leu) which may serve as a dimerization interface. The ZC STE20 subfamily kinases (ZC1, ZC2 and ZC3) have similarly located "PxxP' motifs and potential Leu zippers.

Immediately C-terminal to the proline-rich region of human ZC4 is a 40 amino acid region also predicted to form a coiled-coil structure based on the Lupas algorithm. This region of human ZC4 does not reveal any significant homologies to the protein database.

The 204 amino acid acidic- and serine-rich domain "B" of ZC4 does not reveal any significant homologies to the protein database.

The 355 amino acid C-terminal of human ZC4 is most related to human ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), and ZC2 (SEQ ID NO:14), sharing 43%, 42% and 42% amino acid identity, respectively.

The sequence similarity of the C-terminal region of ZC4 to proteins that have potential Rab- or Rho-binding domains suggests that ZC4, like other ZC-subfamily STE20 kinases, may signal through a small G-protein-dependant pathway.

<u>Mammalian KHS2</u>

The 4023 bp human KHS2 nucleotide sequence encodes a polypeptide of 894 amino acids (SEQ ID NO:18) with a predicted molecular mass of 101,327 daltons. Analysis of the deduced amino acid sequence predicts KHS2 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The full-length KHS2 protein contains a 13 amino acid N-terminus, a 260 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 73 amino acid spacer region, a 188 proline-rich region, followed by a 360 amino acid C-terminal domain containing a potential Rab/Rho-binding site.

KHS2 is most closely related to the human STE20-subfamily kinases KHS1 (GB:U177129), GCK (GB:U07349), and HPK1 (GB:U07349), sharing 65.5%, 51.9%, and 44.9% amino acid identity, respectively and shares 38.5% amino acid identity to a *C. elegans* STK (GB:U55363).

The 13 amino acid N-terminal domain of human KHS2 does not reveal any significant homologies that might suggest a potential function for this domain when examined by a Smith-Waterman alignment to the nonredundant protein database. Human KHS2 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation.

The 260 amino acid catalytic domain of human KHS2 is most related to human STE20-subfamily kinases KHS1 (GB:U177129), GCK (GB:U07349), HPK1 (GB:U66464), SOK-1 (GB:X99325), MST1 (GB:U18297), ZC1 (SEQ ID NO:13), and to the *C. elegans* kinase (GB:U55363), sharing 85.4%, 75.1%, 67.7%, 51.4%, 48.1%, 49.8% and 72.0% amino acid identity, respectively. KHS2 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, ZC3, ZC4, GEK2, SULU1, SULU3, PAK4 and PAK5.

The 73 amino acid acid spacer region of human KHS2 is most related to human STE20-subfamily kinases, KHS1 (GB:U177129), HPK1 (GB:U66464) and GCK (GB:U07349), sharing 60.3%, 43.5% and 44.0%, amino acid identity, respectively.

The 188 amino acid proline-rich region of human KHS2 is most related to human STE20-subfamily kinases, HPK1 (GB:U66464), GCK (GB:U07349) and KHS1 (GB:U177129), sharing 33.3%, 31.9% and 31.4%, amino acid identity, respectively.

Two potential "PxxP" SH3 domain-binding motifs (I and II) are found within the proline-rich region of human KHS2. Motif I is conserved with human KHS1 and HPK1; motif II is

conserved with GCK and KHS2. A 192 amino acid region of human HPK1 containing motif II has been shown to bind to the C-terminal SH3 motif of the adaptor molecule Grb2 (Anafi, M *et al*, J. Biol. Chem. J. 272, 27804-27811 (1997)). Human KHS2 may bind SH3 or WW domain-containing proteins through this proline-rich region.

The 360 amino acid C-terminal of human KHS2 is most related to KHS1 (GB:U177129), GCK (GB:U07349) and HPK1 (GB:U66464), and to the *C. elegans* kinase (GB:U55363), sharing 74.9%, 54.8%, 42.9%, and 31.0%, amino acid identity, respectively. GCK is a STE20-family kinase whose C-terminal domain has been shown to bind the small G-protein Rab8 (Ren, M. *et al*., Proc. Natl. Acad. Sci. 93, 5151-5155 (1996)).

<u>Mammalian SULU1</u>

The 4196 bp human SULU1 nucleotide sequence encodes a polypeptide of 898 amino acids (SEQ ID NO:22) with a predicted molecular mass of 105,402 daltons. Analysis of the deduced amino acid sequence predicts SULU1 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The full-length SULU1 protein contains a 21 amino acid N-terminus, a 256 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 150 amino acid spacer region, a 210 amino acid region predicted to form a coiled-coil structure, a 114 amino acid spacer region and a 147 amino acid C-terminal domain predicted to form a coiled-coil structure.

SULU1 is most closely related to the STE20-subfamily kinases murine SULU3 (SEQ ID NO:24), human SULU3 (SEQ ID NO:23), and to the *C. elegans* kinase SULU (GB:U11280), sharing 68.9%, 72.2% and 38.2% amino acid identity, respectively.

The 21 amino acid N-terminal domain of human SULU1 is most related to murine SULU3 (SEQ ID NO:24) and to the *C. elegans* kinase SULU (GB:U11280), sharing 86.3% and 62.3% amino acid identity. Human SULU1 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristoylation. A Smith-Waterman search of the nonredundant protein database does not reveal any significant homologies that might suggest a potential function for this domain.

The 256 amino acid catalytic domain of human SULU1 is most related to murine SULU3 (SEQ ID NO:24), and to human SOK-1 (GB:X99325), STLK2 (SEQ ID NO:5), MST1 (GB:U18297), PAK1 (GB:U24152), ZC2 (SEQ ID NO:14), and KHS2 (SEQ ID NO:18) sharing 86.3%, 48.1%, 46.9%, 45.2%, 43.3%, 43.1% and 42.0% amino acid identity, respectively. The *C. elegans* SULU STK (GB:U11280) shares 62.3% sequence identity over this region. SULU1 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, ZC3, ZC4, GEK2, KHS2, SULU3, PAK4 and PAK5.

The 150 amino acid spacer region of human SULU1 is most related to human SULU3 (SEQ ID NO:23) and to the *C. elegans* kinase (GB:U11280), sharing 53.5% and 10.4% amino acid identity, respectively.

Immediately C-terminal to the spacer region of human SULU1 is a 210 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of SULU1 is most related to SULU3 (SEQ ID NO:23), the *C. elegans* SULU kinase (GB:U11280), GEK 2 (SEQ ID NO:107) and ZC1 (SEQ ID NO:13), sharing 68.6%,26.8%,23.2%, and 22.8% amino acid identity, respectively.

The 114 amino acid spacer region human SULU1 is most related to human SULU3 (SEQ ID NO:24) with 73.7% amino acid

sequence identity. A lower, yet significant, homology is also evident to murine PITSLRE (GB:U04824) and DLK (GB:A55318), human ZC1 (SEQ ID NO:13) and GEK 2 (SEQ ID NO:107), as well as to *the C. elegans* SULU STK (GB:U11280), sharing 39.7%, 35.4%, 29.5%, 23.6% and 37.6% amino acid identity, respectively.

Immediately C-terminal to the second spacer region of human SULU1 is a 147 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of SULU1 is most related to human SULU3 (SEQ ID NO:24), ZC1 (SEQ ID NO:13) and GEK 2 (SEQ ID NO:107), as well as to the *C. elegans* SULU STK (GB:U11280), sharing 73.3%, 28.4%, 26.1% and 39.5%, amino acid identity, respectively.

<u>Mammalian (human) SULU3</u>

The 3824 bp partial cDNA human SULU3 nucleotide sequence encodes a polypeptide of 786 amino acids (SEQ ID NO:23) with a predicted molecular mass of 92,037 daltons. Analysis of the deduced amino acid sequence predicts SULU3 to be an intracellular serine/threonine kinase lacking a transmembrane domain. The N-terminally truncated human SULU3 protein contains a 66 amino acid partial catalytic domain followed by a 149 amino acid spacer region, a 210 amino acid region predicted to form a coiled-coil structure, a second spacer region of 114 amino acids, a 247 amino acid C-terminal region predicted to form a second coiled-coil structure and a 100 amino acid C-terminal tail.

Human SULU3 is most closely related murine SULU3 (SEQ ID NO:24), human SULU1 (SEQ ID NO:22), and to the C. *elegans* SULU kinase (GB:U11280), sharing 66.3%, 68.9% and 32.9% amino acid identity, respectively. The high sequence

homology between murine and human SULU3 suggests that these two proteins are orthologs of each other.

The 66 amino acid partial catalytic domain of human SULU3 is most related to murine SULU3 (SEQ ID NO:24), and to the human STE20 subfamily kinases ZC1 (SEQ ID NO:13), STE20 (GB:X99325), KHS1(GB:U177129) and GEK 2 (SEQ ID NO:107), as well as to the C. *elegans* SULU kinase (GB:U11280), sharing 83.3%, 47.0%, 45.5%, 43.5%,41.8% and 55.6% amino acid identity, respectively.

The 149 amino acid spacer region of human SULU3 is most related to murine SULU3 (SEQ ID NO:24), human STE20 (GB:X99325), MST1 (GB:U18297), and to the *C.elegans* SULU kinase (GB:U11280) sharing 98.7%, 21.9% and 21.8% amino acid identity, respectively.

Immediately C-terminal to the first spacer region of human SULU3 is a 210 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of SULU3 is most related to murine SULU3 (SEQ ID NO:24), and to human SULU1 (SEQ ID NO:22), ZC1 (SEQ ID NO:13) and GEK 2 (SEQ ID NO:107), as well as to the *C. elegans* SULU kinase (GB:U11280), sharing 99. 5%, 68.6%, 27.4% and 22.5% amino acid identity, respectively.

The 114 amino acid second spacer region of human SULU3 is most related to murine SULU3 (SEQ ID NO:24), and to human SULU1 (SEQ ID NO:22) GEK 2 (SEQ ID NO:107), and ZC1 (SEQ ID NO:13), as well as to the *C. elegans* SULU kinase (GB:U11280), sharing 99.1%, 73.7%, 24.6%,24.1% and 41.2% amino acid identity, respectively.

Immediately C-terminal to the second spacer region of human SULU3 is a 247 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (supra). This region of SULU3 is most related to human SULU1 (SEQ ID NO:22) and ZC1 (SEQ ID NO:13) as well as to rat PKN-

(GB:D26180) murine p160 ROCK1 (GB:U58512), and the *C. elegans* SULU kinase (GB:U11280), sharing 73.7%, 26.7%, 24.0% and 21.0% amino acid identity, respectively.

The 100 amino acid C-tail of human SULU3 is most related to a human prion protein (GB:L38993), with 45.0% amino acid identity.

Mammalian (murine) SULU3

The 2249 bp murine, partial cDNA SULU3 nucleotide sequence encodes a polypeptide of 748 amino acids (SEQ ID NO:24) with a predicted molecular mass of 87,520 daltons. Analysis of the deduced amino acid sequence predicts SULU3 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The partial murine SULU3 protein contains a 25 amino acid N-terminus, a 248 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 149 amino acid spacer region, a 210 amino acid region predicted to form a coiled-coil structure, and a 116 amino acid spacer region.

Murine SULU3 is most closely related to human SULU3 (SEQ ID NO:23) and SULU1 (SEQ ID NO:22), as well as to the *C. elegans* SULU kinase (GB:U112 80), sharing 97.0%, 72.3% and 38.4% amino acid identity, respectively. The high sequence homology between murine and human SULU3 suggests that these two proteins are orthologs.

The 25 amino acid N-terminal domain of murine SULU3 is most related to human SULU1 (SEQ ID NO:22) and to the *C. elegans* SULU kinase (GB:U11280), sharing 70.0% and 44.4% amino acid identity, respectively.

Murine SULU3 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristoylation. A Smith-Waterman search of the nonredundant protein database does

not reveal any significant homologies that might suggest a potential function for this domain.

The 248 amino acid catalytic domain of murine SULU3 is most related to human SULU1 (SEQ ID NO:22), STE20 (GB:X99325), ZC1 (SEQ ID NO:13), and KHS1 (GB:U77129), as well as to the *C. elegans* SULU kinase (GB:U11280), sharing 86.7%, 46.6%, 43.3%, 59.4% amino acid identity, respectively. Murine SULU3 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

The 149 amino acid spacer of murine SULU3 is most related to human SULU3 (SEQ ID NO:23), SULU1 (SEQ ID NO:22), and STE20 (GB:X99325), as well as to the *C . elegans* SULU (GB:U11280) and the *S. cerevisiae* STE20 (GB:L04655) kinases, sharing 98.7%, 53.4%, 21.9%, 59.4% and 21.9% amino acid identity, respectively.

Immediately C-terminal to the spacer region of murine SULU3 is a 210 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of murine SULU3 is most related to human SULU3 (SEQ ID NO:23), ZC1 (SEQ ID NO:13), and GEK 2 (SEQ ID NO:107), as well as to the C. *elegans* SULU kinase (GB:U11280), sharing 99.5%, 27.4%, 22.5% and 29.2% amino acid identity, respectively.

The 116 amino acid C-terminal spacer region of murine SULU3 is most related to human SULU3 (SEQ ID NO:23), GEK 2 (SEQ ID NO:107), and ZC1 (SEQ ID NO:13), well as to the *C. elegans* SULU kinase (GB:U11280), sharing 98.3%, 24.6%, 24.1% and 40.5% amino acid identity, respectively.

Mammalian (murine/human) SULU3

The 2249 bp murine SULU3 and the 3824 bp human SULU3 cDNAs contain a 1620 nucleotide overlap (541 amino acids) with 90% and 98% DNA and amino acid sequence identity, respectively. Owing to the high degree of sequence identity in this extended overlap, we propose that these are functional orthologues of a single gene. The combined murine/human 4492 bp SULU3 sequence encodes a polypeptide of 1001 amino acids (SEQ ID NO:31) with a predicted molecular mass of 116,069 daltons. Analysis of the deduced amino acid sequence predicts SULU3 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. SULU3 contains a 25 amino acid N-terminus, a 248 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 149 amino acid spacer region, a 210 amino acid region predicted to form a coiled-coil structure and a second spacer region of 114 amino acids, a 247 amino acid C-terminal region predicted to form a second coiled-coil structure and a 100 amino acid C-terminal tail. The murine SULU3 clone lacks the region from the second C-terminal coiled-coil to the C-terminus, whereas the human clone lacks the N-terminal domain, and all but 66 amino acids of the 248 amino acid kinase domain.

SULU3 is most closely related to SULU1 (SEQ ID NO:22) and the *C. elegans* SULU kinase (GB:U11280) sharing 72.3% and 38.4% amino acid identity, respectively.

The 25 amino acid N-terminal domain of SULU3 is most related to human SULU1 (SEQ ID NO:22) and to the *C. elegans* SULU kinase (GB:U11280), sharing 70.0% and 44.4% amino acid identity, respectively. SULU3 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation. A Smith-Waterman search of the nonredundant

protein database does not reveal any significant homologies that might suggest a potential function for this domain.

The 248 amino acid catalytic domain of SULU3 is most related to human SULU1 (SEQ ID NO:22), SOK-1 (GB:X99325), ZC1 (SEQ ID NO:13), KHS1 (GB:U77129) and the *C. elegans* SULU kinase (GB:U11280), sharing 86.7%, 46.6%, 43.3%, 42.0% and 59.4% amino acid identity, respectively. SULU3 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, PAK4 and PAK5.

The 149 amino acid spacer of SULU3 is most related to SULU1 (SEQ ID NO:22) and SOK-1 (GB:X99325), and to the *C. elegans* SULU (GB:U11280), and *S. cerevisiae* STE20 (GB:L04655) kinases, sharing 53.4%, 21.9%, 59.4% and 21.9% amino acid identity, respectively.

Immediately C-terminal to the spacer region of SULU3 is a 210 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region is most related to ZC1 (SEQ ID NO:13), GEK 2 (SEQ ID NO:107), and the *C. elegans* SULU kinase (GB:U11280), sharing 27.4% 22.5% and 29.2% amino acid identity, respectively.

The 114 amino acid spacer region of SULU3 is most related to human SULU1 (SEQ ID NO:22), GEK 2 (SEQ ID NO:107), ZC1 (SEQ ID NO:13), and to the *C. elegans* SULU kinase (GB:U11280), sharing 73.7%, 24.6%, 24.1% and 41.2% amino acid identity, respectively.

Immediately C-terminal to the second spacer region of SULU3 is a 247 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of SULU3 is most related to human SULU1 (SEQ ID NO:22) and ZC1 (SEQ ID NO:13), as well as to rat PKN (GB:D26180), murine p160 ROCK1 (GB:U58512) and the *C. elegans* SULU kinase

(GB:U11280), sharing 73.7%, 26.7%, 24.0%, 21.0% and 37.6% amino acid identity, respectively.

The 100 amino acid C-tail of SULU3 is most related to a human prion protein (GB:L38993) with 45.0% amino acid identity.

Mammalian GEK2

The 2926 bp human GEK2 nucleotide sequence of the complete cDNA encodes a polypeptide of 968 amino acids (SEQ ID NO:107) with a predicted molecular mass of 112,120 daltons. Analysis of the deduced amino acid sequence predicts GEK2 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The complete GEK2 protein contains a 33 amino acid N-terminus, a 261 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 43 amino acid spacer region, a 135 amino acid proline-rich region, a 252 amino acid region predicted to form a coiled-coil structure followed by a 244 amino acid region also predicted to form a coiled-coil structure.

GEK2 is most closely related to rat AT1-46 (GB:U33472) (a partial cDNA that extends from the middle of the first potential coiled-coil domain of GEK2 to the C-terminus), murine LOK (GB:D89728), *Xenopus laevis* polo-like kinase 1 (GB:AF100165), and human SLK (GB:AB002804), sharing 91.3%, 88.5%, 65.0%, and 44.7% amino acid identity, respectively. The high sequence homology between human GEK2, murine LOK and rat AT1-46 suggests that human GEK2 is a highly related protein to the rodent forms, or alternatively, its orthologue. Recently, a full-length version of GEK2 was reported (STK10 or human LOK AB015718). The 968 amino acid sequence is 99% identical to GEK2 (SEQ ID NO:107).

The 33 amino acid N-terminal domain of human GEK2 is most related to murine LOK (GB:D89728) and to human SLK (GB:AB002804), sharing 100% and 54.5% amino acid identity, respectively.

Human GEK2 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation. A Smith-Waterman search of the nonredundant protein database does not reveal any significant homologies that might suggest a potential function for this domain.

The 261 amino acid catalytic domain of human GEK2 is most related to murine LOK (GB:D89728), rat AT1-46 (GB:D89728) and human SLK (GB:AB002804) as well as to a *C. elegans* kinase (GB:Z81460), sharing 97.7%, 90.8%, 54.5% and 55.9% amino acid identity, respectively. GEK2 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

The 43 amino acid spacer region of human GEK2 is most related to murine LOK (GB:D89728) and to human SLK, sharing 83.7% and 77.6% amino acid identity, respectively.

The 135 amino acid proline-rich region of human GEK2 is most related to murine LOK (GB:D89728) with 66.2% amino acid identity, respectively. Within the proline-rich region of human GEK2 is a potential "PxxP" SH3-binding domain conserved with murine LOK.

Immediately C-terminal to the proline-rich region of human GEK2 is a 252 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of human GEK2 is most related to rat AT1-46 (GB:D89728), murine LOK (GB:D89728) and human SLK (GB:AB002804), and ZC2 (SEQ ID NO:14), sharing 90.8%, 86.9%, 42.2%, and 29.7% amino acid identity, respectively.

Immediately C-terminal to the predicted coiled-coil structure of human GEK2 is a second potential coiled-coil structure of 244 amino acids predicted based on the Lupas algorithm. This region of human GEK2 is most related to rat AT1-46 (GB:D89728) and murine LOK (GB:D89728) as well as to human SLK (GB:AB002804) and ZC1 (SEQ ID NO:13), sharing 91.8%, 92.6%, 70.4% and 26.7% amino acid identity, respectively. The *C. elegans* kinase (GB:Z81460) shares 31.5% amino acid sequence identity over this region.

Mammalian PAK4

The 3604 bp human PAK4 nucleotide sequence encodes a polypeptide of 681 amino acids (SEQ ID NO:29) with a predicted molecular mass of 74,875 daltons. Analysis of the deduced amino acid sequence predicts PAK4 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The full-length PAK4 protein contains a 51 amino acid N-terminus predicted to contain a rac-binding motif, a 173 amino acid insert relative to the known mammalian PAK proteins, a 169 amino acid spacer region, a 265 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase and a 23 amino acid C-terminal tail.

PAK4 is most closely related to human PAK5 (SEQ ID NO:30), PAK1 (GB: U24152), and PAK65 (GB:U25975), as well as to a *C. elegans* kinase (GB: Z74029), sharing 76.8%, 49.5%, 49.8%, and 34.6% amino acid identity, respectively.

The 51 amino acid N-terminal domain of human PAK4 is most related to human PAK1 (GB:U24152), and PAK65 (GB:U25975), as well as to a *C.elegans* kinase (GB: Z74029), sharing 50.0%, 50.0% and 49.0% amino acid identity, respectively.

The 11 amino acid region at positions 13-23 of human PAK4 fits the consensus for a Cdc42/Rac-binding motif (SXPX4-6HXXH) (Burbelo, P.D., Dreschel, D. and Hall, A. J. Bio. Chem. 270, 29071-29074 (1995)).

The 173 amino acid insert of human PAK4, relative to the known mammalian PAK proteins, is most related to a *C. elegans* kinase (GB: Z74029) with 39.0% amino acid identity. A Smith-Waterman search of the nonredundant protein database does not reveal any significant homologies that might suggest a potential function for this region.

The 169 amino acid spacer of human PAK4 does not reveal any significant homologies that might suggest a potential function for this region.

The equivalent spacer region in PAK1 binds to the guanine nucleotide exchange factor PIX (Manser, E. *et al* (1998) Molecular Cell, 1, 183-192). Since PAK4 differs substantially from PAK1 over this region, the spacer domain of PAK4 may differ in its guanine nucleotide exchange factor binding specificity, relative to PAK1.

The 265 amino acid catalytic domain of human PAK4 is most related to human PAK5 (SEQ ID NO:30), PAK1 (GB:U24152), GCK (GB:U07349), SOK-1 (GB:X99325), and SLK (GB:AB002804), as well as to the *C. elegans* (GB: Z74029), and *S. cerevisiae* STE20-related kinases (GB:L04655), sharing 95.9%, 51.7%, 41.3%, 39.8%, 37.4%, 60.2% and 47.9% amino acid identity, respectively. PAK4 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3 and PAK5.

The 23 amino acid C-tail of human PAK4 contains a sequence that is homologous to a G-protein beta subunit binding site (Leeuw, T. *et al*. Nature, 391, 191-195 (1998)).

PAK4 has, therefore, the potential to be activated by both Cdc42- as well as G-protein-dependant pathways.

Mammalian PAK5

The 2,806 bp human PAK5 nucleotide sequence of the complete cDNA encodes a polypeptide of 591 amino acids (SEQ ID NO:103) with a predicted molecular mass of 64,071 Daltons. Analysis of the deduced amino acid sequence predicts PAK5 to be an intracellular STE20-subfamily kinase, lacking both a signal sequence and transmembrane domain. The full-length PAK5 protein contains a 52 amino acid N-terminus predicted to contain a p21 (small G-protein) binding domain (PDB or CRIB), a 121 amino acid insert relative to the known mammalian PAK proteins, a 134 amino spacer region, a 265 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase and a 19 amino acid C-terminal tail.

PAK5 is most closely related to Human PAK4 (SEQ ID NO:29), *Drosophila melanogaster* PAK (also known as "mushroom bodies tiny") (AJ011578), C45B11.1b from *C. elegans* (Z74029), and human PAK3 (Q13177) sharing 48% (327/674 aa), 50% (330/651 aa), 43% (234/435 aa excluding gap), and 47% (190/405 aa excluding gap) amino acid identity, respectively. Recently, a full length version of PAK5 was reported (PAK4 AF005046) whose 591 amino acid sequence is identical to PAK5 (SEQ ID NO:103). (Abo, *et al.* (1998) EMBO J. 17:6527-6540).

The 52 amino acid N-terminal domain of human PAK5 is most related to human PAK4 (SEQ ID NO:29), *Drosophila melanogaster* PAK (AJ011578), C45B11.1b from *C. elegans* (Z74029), and human PAK3 (Q13177), sharing 65%, 57%, 54%, and 53% amino acid identity, respectively.

The 11 amino acid region at positions 12-22 of human PAK5 (FIG. 18) fits the consensus for a small G-protein binding domain (PDB or CRIB) (SXPX4-6HXXH) (Burbelo, P.D., Dreschel, D. and Hall, A. J. Bio. Chem. 270, 29071-29074 (1995), hereby incorporated by reference herein in its entirety including any figures, tables, or drawings.).

The 121 amino acid insert of human PAK5 shares 43% amino acid identity with a similar domain from PAK4 (SEQ ID NO:29), but that is absent from other known PAKs.

The equivalent spacer region in PAK1 binds to the guanine nucleotide exchange factor PIX (Manser, E. et al (1998) Molecular Cell, 1, 183-192 hereby incorporated by reference herein in its entirety including any drawings, figures, or tables.). Since PAK5 differs substantially from PAK1 over this region, the spacer domain of PAK5 may differ in its guanine nucleotide exchange factor binding specificity, relative to PAK1.

The 134 amino acid collagen-like region of human PAK5 shares 34% amino acid identity to pro-α I type collagen from several species and is not present in other known PAKs.

The 265 amino acid catalytic domain of human PAK5 is most related to human PAK4 (SEQ ID NO:29), *Drosophila melanogaster* PAK (AJ011578), C45B11.1b from *C. elegans* (Z74029), and human PAK3 (Q13177), sharing 78%, 80%, 61%, and 55% amino acid identity, respectively. PAK5 also contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3 and PAK4.

The 19 amino acid C-tail shares 80% amino acid identity to a PAK-like homologue identified from genomic DNA (AL031652). Furthermore, this C-terminal region of human PAK5 contains a sequence that is homologous to a G-protein

beta subunit binding site (Leeuw, T. et al. Nature, 391, 191-195 (1998) hereby incorporated by reference herein in its entirety including any figures, tables, or drawings).. PAK5 has, therefore, the potential to be activated by both, Cdc42 as well as G-protein-dependant pathways.

V. Antibodies, Hybridomas, Methods of Use and Kits for Detection of STE20-Related Kinases

The present invention relates to an antibody having binding affinity to a kinase of the invention. The polypeptide may have the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or a functional derivative thereof, or at least 9 contiguous amino acids thereof (preferably, at least 20, 30, 35, or 40 or more contiguous amino acids thereof).

The present invention also relates to an antibody having specific binding affinity to a kinase of the invention. Such an antibody may be isolated by comparing its binding affinity to a kinase of the invention with its binding affinity to other polypeptides. Those which bind selectively to a kinase of the invention would be chosen for use in methods requiring a distinction between a kinase of the invention and other polypeptides. Such methods could include, but should not be limited to, the analysis of altered kinase expression in tissue containing other polypeptides.

The STE20-Related kinases of the present invention can be used in a variety of procedures and methods, such as for the generation of antibodies, for use in identifying

pharmaceutical compositions, and for studying DNA/protein interaction.

The kinases of the present invention can be used to produce antibodies or hybridomas. One skilled in the art will recognize that if an antibody is desired, such a peptide could be generated as described herein and used as an immunogen. The antibodies of the present invention include monoclonal and polyclonal antibodies, as well fragments of these antibodies, and humanized forms. Humanized forms of the antibodies of the present invention may be generated using one of the procedures known in the art such as chimerization or CDR grafting.

The present invention also relates to a hybridoma which produces the above-described monoclonal antibody, or binding fragment thereof.. A hybridoma is an immortalized cell line which is capable of secreting a specific monoclonal antibody.

In general, techniques for preparing monoclonal antibodies and hybridomas are well known in the art (Campbell, "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology," Elsevier Science Publishers, Amsterdam, The Netherlands, 1984; St. Groth *et al.*, J. Immunol. Methods 35:1-21, 1980). Any animal (mouse, rabbit, and the like) which is known to produce antibodies can be immunized with the selected polypeptide. Methods for immunization are well known in the art. Such methods include subcutaneous or intraperitoneal injection of the polypeptide. One skilled in the art will recognize that the amount of polypeptide used for immunization will vary based on the animal which is immunized, the antigenicity of the polypeptide and the site of injection.

The polypeptide may be modified or administered in an adjuvant in order to increase the peptide antigenicity. Methods of increasing the antigenicity of a polypeptide are well known in the art. Such procedures include coupling the antigen with a heterologous protein (such as globulin or β-galactosidase) or through the inclusion of an adjuvant during immunization.

For monoclonal antibodies, spleen cells from the immunized animals are removed, fused with myeloma cells, such as SP2/0-Ag14 myeloma cells, and allowed to become monoclonal antibody producing hybridoma cells. Any one of a number of methods well known in the art can be used to identify the hybridoma cell which produces an antibody with the desired characteristics. These include screening the hybridomas with an ELISA assay, western blot analysis, or radioimmunoassay (Lutz *et al.*, Exp. Cell Res. 175:109-124, 1988). Hybridomas secreting the desired antibodies are cloned and the class and subclass are determined using procedures known in the art (Campbell, "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology", supra, 1984).

For polyclonal antibodies, antibody-containing antisera is isolated from the immunized animal and is screened for the presence of antibodies with the desired specificity using one of the above-described procedures. The above-described antibodies may be detectably labeled. Antibodies can be detectably labeled through the use of radioisotopes, affinity labels (such as biotin, avidin, and the like), enzymatic labels (such as horse radish peroxidase, alkaline phosphatase, and the like) fluorescent labels (such as FITC or rhodamine, and the like), paramagnetic atoms, and the like. Procedures for accomplishing such labeling are well-known in the art, for example, *see* Stemberger *et al.*, J.

Histochem. Cytochem. 18:315, 1970; Bayer *et al.*, Meth. Enzym. 62:308-, 1979; Engval *et al.*, Immunol. 109:129-, 1972; Goding, J. Immunol._Meth. 13:215-, 1976. The labeled antibodies of the present invention can be used for *in vitro, in vivo*, and *in situ* assays to identify cells or tissues which express a specific peptide.

The above-described antibodies may also be immobilized on a solid support. Examples of such solid supports include plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, acrylic resins and such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art (Weir *et al.*, "Handbook of Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford, England, Chapter 10, 1986; Jacoby *et al.*, Meth. Enzym. 34, Academic Press, N.Y., 1974). The immobilized antibodies of the present invention can be used for *in vitro, in vivo*, and *in situ* assays as well as in immunochromotography.

Furthermore, one skilled in the art can readily adapt currently available procedures, as well as the techniques, methods and kits disclosed herein with regard to antibodies, to generate peptides capable of binding to a specific peptide sequence in order to generate rationally designed antipeptide peptides (Hurby *et al.*, "Application of Synthetic Peptides: Antisense Peptides", In Synthetic Peptides, A User's Guide, W.H. Freeman, NY, pp. 289-307, 1992; Kaspczak *et al.*, Biochemistry 28:9230-9238, 1989).

Anti-peptide peptides can be generated by replacing the basic amino acid residues found in the peptide sequences of the kinases of the invention with acidic residues, while maintaining hydrophobic and uncharged polar groups. For example, lysine, arginine, and/or histidine residues are

replaced with aspartic acid or glutamic acid and glutamic acid residues are replaced by lysine, arginine or histidine.

The present invention also encompasses a method of detecting a STE20-related kinase polypeptide in a sample, comprising: (a) contacting the sample with an above-described antibody, under conditions such that immunocomplexes form, and (b) detecting the presence of said antibody bound to the polypeptide. In detail, the methods comprise incubating a test sample with one or more of the antibodies of the present invention and assaying whether the antibody binds to the test sample. Altered levels of a kinase of the invention in a sample as compared to normal levels may indicate disease.

Conditions for incubating an antibody with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the antibody used in the assay. One skilled in the art will recognize that any one of the commonly available immunological assay formats (such as radioimmunoassays, enzyme-linked immunosorbent assays, diffusion based Ouchterlony, or rocket immunofluorescent assays) can readily be adapted to employ the antibodies of the present invention. Examples of such assays can be found in Chard ("An Introduction to Radioimmunoassay and Related Techniques" Elsevier Science Publishers, Amsterdam, The Netherlands, 1986), Bullock *et al.* ("Techniques in Immunocytochemistry," Academic Press, Orlando, FL Vol. 1, 1982; Vol. 2, 1983; Vol. 3, 1985), Tijssen ("Practice and Theory of Enzyme Immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology," Elsevier Science Publishers, Amsterdam, The Netherlands, 1985).

The immunological assay test samples of the present invention include cells, protein or membrane extracts of

cells, or biological fluids such as blood, serum, plasma, or urine. The test samples used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is testable with the system utilized.

A kit contains all the necessary reagents to carry out the previously described methods of detection. The kit may comprise: (i) a first container means containing an above-described antibody, and (ii) second container means containing a conjugate comprising a binding partner of the antibody and a label. In another preferred embodiment, the kit further comprises one or more other containers comprising one or more of the following: wash reagents and reagents capable of detecting the presence of bound antibodies.

Examples of detection reagents include, but are not limited to, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the chromophoric, enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. The compartmentalized kit may be as described above for nucleic acid probe kits. One skilled in the art will readily recognize that the antibodies described in the present invention can readily be incorporated into one of the established kit formats which are well known in the art.

VI. Isolation of Compounds Which Interact With STE20-Related Kinases

The present invention also relates to a method of detecting a compound capable of binding to a STE20-related kinase of the invention comprising incubating the compound with a kinase of the invention and detecting the presence of the compound bound to the kinase. The compound may be present within a complex mixture, for example, serum, body fluid, or cell extracts.

The present invention also relates to a method of detecting an agonist or antagonist of kinase activity or kinase binding partner activity comprising incubating cells that produce a kinase of the invention in the presence of a compound and detecting changes in the level of kinase activity or kinase binding partner activity. The compounds thus identified would produce a change in activity indicative of the presence of the compound. The compound may be present within a complex mixture, for example, serum, body fluid, or cell extracts. Once the compound is identified it can be isolated using techniques well known in the art.

The present invention also encompasses a method of agonizing (stimulating) or antagonizing kinase associated activity in a mammal comprising administering to said mammal an agonist or antagonist to a kinase of the invention in an amount sufficient to effect said agonism or antagonism. A method of treating diseases in a mammal with an agonist or antagonist of STE20-related kinase activity comprising administering the agonist or antagonist to a mammal in an amount sufficient to agonize or antagonize STE20-related kinase associated functions is also encompassed in the present application.

In an effort to discover novel treatments for diseases, biomedical researchers and chemists have designed, synthesized, and tested molecules that inhibit the function of protein kinases. Some small organic molecules form a class of compounds that modulate the function of protein kinases. Examples of molecules that have been reported to inhibit the function of protein kinases include, but are not limited to, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT WO 92/20642, published November 26, 1992 by Maguire *et al.*), vinylene-azaindole derivatives (PCT WO 94/14808, published July 7, 1994 by Ballinari *et al.*), 1-cyclopropyl-4-pyridyl-quinolones (U.S. Patent No. 5,330,992), styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1), seleoindoles and selenides (PCT WO 94/03427, published February 17, 1994 by Denny *et al.*), tricyclic polyhydroxylic compounds (PCT WO 92/21660, published December 10, 1992 by Dow), and benzylphosphonic acid compounds (PCT WO 91/15495, published October 17, 1991 by Dow *et al*).

Compounds that can traverse cell membranes and are resistant to acid hydrolysis are potentially advantageous as therapeutics as they can become highly bioavailable after being administered orally to patients. However, many of these protein kinase inhibitors only weakly inhibit the function of protein kinases. In addition, many inhibit a variety of protein kinases and will cause multiple side-effects as therapeutics for diseases.

Some indolinone compounds, however, form classes of acid resistant and membrane permeable organic molecules. WO 96/22976 (published August 1, 1996 by Ballinari *et al.*) describes hydrosoluble indolinone compounds that harbor

tetralin, naphthalene, quinoline, and indole substituents fused to the oxindole ring. These bicyclic substituents are in turn substituted with polar moieties including hydroxylated alkyl, phosphate, and ether moieties. U.S. Patent Application Serial Nos. 08/702,232, filed August 23, 1996, entitled "Indolinone Combinatorial Libraries and Related Products and Methods for the Treatment of Disease" by Tang *et al.* (Lyon & Lyon Docket No. 221/187) and 08/485,323, filed June 7, 1995, entitled "Benzylidene-Z-Indoline Compounds for the Treatment of Disease" by Tang *et al.* (Lyon & Lyon Docket No. 223/298) and International Patent Publication WO 96/22976, published August 1, 1996 by Ballinari *et al.*, all of which are incorporated herein by reference in their entirety, including any drawings, describe indolinone chemical libraries of indolinone compounds harboring other bicyclic moieties as well as monocyclic moieties fused to the oxindole ring. Applications 08/702,232, filed August 23, 1996, entitled "Indolinone Combinatorial Libraries and Related Products and Methods for the Treatment of Disease" by Tang *et al.* (Lyon & Lyon Docket No. 221/187), 08/485,323, filed June 7, 1995, entitled "Benzylidene-Z-Indoline Compounds for the Treatment of Disease" by Tang *et al.* (Lyon & Lyon Docket No. 223/298), and WO 96/22976, published August 1, 1996 by Ballinari *et al.* teach methods of indolinone synthesis, methods of testing the biological activity of indolinone compounds in cells, and inhibition patterns of indolinone derivatives.

Other examples of substances capable of modulating kinase activity include, but are not limited to, tyrphostins, quinazolines, quinoxolines, and quinolines. The quinazolines, tyrphostins, quinolines, and quinoxolines referred to above include well known compounds such as those described in the literature. For example, representative

publications describing quinazolines include Barker et al., EPO Publication No. 0 520 722 A1; Jones et al., U.S. Patent No.4,447,608; Kabbe et al., U.S. Patent No. 4,757,072; Kaul and Vougioukas, U.S. Patent No. 5, 316,553; Kreighbaum and Comer, U.S. Patent No. 4,343,940; Pegg and Wardleworth, EPO Publication No. 0 562 734 A1; Barker et al., Proc. of Am. Assoc. for Cancer Research 32:327 (1991); Bertino, J.R., Cancer Research 3:293-304 (1979); Bertino, J.R., Cancer Research 9(2 part 1):293-304 (1979); Curtin et al., Br. J. Cancer 53:361-368 (1986); Fernandes et al., Cancer Research 43:1117-1123 (1983); Ferris et al. J. Org. Chem. 44(2):173-178; Fry et al., Science 265:1093-1095 (1994); Jackman et al., Cancer Research 51:5579-5586 (1981); Jones et al. J. Med. Chem. 29(6):1114-1118; Lee and Skibo, Biochemistry 26(23):7355-7362 (1987); Lemus et al., J. Org. Chem. 54:3511-3518 (1989); Ley and Seng, Synthesis 1975:415-522 (1975); Maxwell et al., Magnetic Resonance in Medicine 17:189-196 (1991); Mini et al., Cancer Research 45:325-330 (1985); Phillips and Castle, J. Heterocyclic Chem. 17(19):1489-1596 (1980); Reece et al., Cancer Research 47(11):2996-2999 (1977); Sculier et al., Cancer Immunol. and Immunother. 23:A65 (1986); Sikora et al., Cancer Letters 23:289-295 (1984); Sikora et al., Analytical Biochem. 172:344-355 (1988); all of which are incorporated herein by reference in their entirety, including any drawings.

Quinoxaline is described in Kaul and Vougioukas, U.S. Patent No. 5,316,553, incorporated herein by reference in its entirety, including any drawings.

Quinolines are described in Dolle et al., J. Med. Chem. 37:2627-2629 (1994); MaGuire, J. Med. Chem. 37:2129-2131 (1994); Burke et al., J. Med. Chem. 36:425-432 (1993); and Burke et al. BioOrganic Med. Chem. Letters 2:1771-1774

(1992), all of which are incorporated by reference in their entirety, including any drawings.

Tyrphostins are described in Allen et al., Clin. Exp. Immunol. 91:141-156 (1993); Anafi et al., Blood 82:12:3524-3529 (1993); Baker et al., J. Cell Sci. 102:543-555 (1992); Bilder et al., Amer. Physiol. Soc. pp. 6363-6143:C721-C730 (1991); Brunton et al., Proceedings of Amer. Assoc. Cancer Rsch. 33:558 (1992); Bryckaert et al., Experimental Cell Research 199:255-261 (1992); Dong et al., J. Leukocyte Biology 53:53-60 (1993); Dong et al., J. Immunol. 151(5):2717-2724 (1993); Gazit et al., J. Med. Chem. 32:2344-2352 (1989); Gazit et al., " J. Med. Chem. 36:3556-3564 (1993); Kaur et al., Anti-Cancer Drugs 5:213-222 (1994); Kaur et al., King et al., Biochem. J. 275:413-418 (1991); Kuo et al., Cancer Letters 74:197-202 (1993); Levitzki, A., The FASEB J. 6:3275-3282 (1992); Lyall et al., J. Biol. Chem. 264:14503-14509 (1989); Peterson et al., The Prostate 22:335-345 (1993); Pillemer et al., Int. J. Cancer 50:80-85 (1992); Posner et al., Molecular Pharmacology 45:673-683 (1993); Rendu et al., Biol. Pharmacology 44(5):881-888 (1992); Sauro and Thomas, Life Sciences 53:371-376 (1993); Sauro and Thomas, J. Pharm. and Experimental Therapeutics 267(3):119-1125 (1993); Wolbring et al., J. Biol. Chem. 269(36):22470-22472 (1994); and Yoneda et al., Cancer Research 51:4430-4435 (1991); all of which are incorporated herein by reference in their entirety, including any drawings.

Other compounds that could be used as modulators include oxindolinones such as those described in U.S. patent application Serial No. 08/702,232 filed August 23, 1996, incorporated herein by reference in its entirety, including any drawings.

VII. Biological Significance, Applications and Clinical Relevance of Novel STE20-Related Kinases

Human STLK2, STLK3, STLK4, STLK5, STLK6, and STLK7

STLK2, STLK4, STLK5, STLK6 and STLK7 belong to an expanding family of intracellular STKs that have varying degrees of sequence homology to SOK-1, a kinase implicated in oxidative stress agents (Pombo, CM et al, EMBO J. (17) 4537-4546, 1996). Our data shows that STLK2 is expressed highly in hematopoietic cells. Therefore, STLK2 may participate in the oxidative response pathway during inflammation. In addition, STLK2 could also be a possible component in the signaling pathways leading to T cell activation. High levels of STLK2 in several tumor cell lines could also imply that STLK2 might be involved in tumorigenesis.

STLK2 is most closely related to two human STE20-subfamily kinases: MST3 and SOK-1. MST3 is a 52,000 daltons cytoplasmic kinase that is ubiquitously expressed with its highest levels of expression found in heart, skeletal muscle and pancreas. The serine/threonine kinase activity of MST3 is activated by phosphorylation. Unlike SOK-1, MST3 prefers Mn^{++} over Mg^{++} and can use both GTP and ATP as phosphate donors. MST3 may undergo dimerization. No agonists have yet been identified that activate MST3. The downstream signaling mechanism of this kinase is unknown (Schinkmann, K and Blenis, J. (1997) J. Biol. Chem. 272, 28695-28703).

SOK-1 is a 50,000 daltons cytoplasmic kinase expressed predominantly in testis, large intestine, brain and stomach and to a lesser extent in heart and lung. SOK-1 is also expressed in the germinal center B-cell line (RAMOS) and in a mature B cell line (HS Sultan). The serine/threonine kinase activity of SOK-1 is activated by phosphorylation.

The C-terminus of SOK-1 has been shown to be inhibitory to the catalytic activity of this kinase. The only agonists known to activate SOK-1 are oxidant agents, like H_2O_2 and menadione, a quinone that is a potent intracellular generator of reactive oxygen species (Pombo, C.M. *et al.* EMBO J. 15, 4537-4546). SOK-1 is also activated by chemical anoxia through the generation of reactive oxygen species and release of calcium into the cytoplasm from intracellular stores. SOK-1, therefore, may play an important role in ischemia, the cause of myocardial infarction, stroke and acute renal failure (Pombo, C.M. *et al.* J. Biol. Chem. 272, 29372-29379 (1997)). The activity of SOK-1 in the response to oxidant stress is inversely correlated with the activity of the stress-activated protein kinases (SAPKs): elevated SOK-1 activity correlates with absent SAPK activity and vice-versa. SOK-1 does not activate any of the four MAP kinase pathways, SAPKs, p38, ERK-1 or MEK-5/ERK-5 (Pombo, C.M. *et al.* EMBO J. 15, 4537-4546). The downstream signaling mechanism of this kinase remains unknown.

STLK2 is expressed in a wide variety of immune cell types and tissues including thymus, dendrocytes, mast cells, monocytes, B cells (primary, Jurkat, RPMI, SR), T cells (CD8/CD4+, TH1, TH2, CEM, MOLT4) and megakaryocytes (K562), whereas STLK3 is restricted to thymus and STLK4 is predominately expressed in thymus, T cells (CD4/CD8+, TH1, CEM) and B cells (Jurkat, RPMI). Consequently, these STKs might participate in the oxidative response pathway during inflammation, reperfusion injury (stroke, surgery, shock), TNFα-mediated signaling, insulin desensitization, atherogenesis, vascular injury, T or B cell costimulation, or alternatively, participate in other MAPK-related signal transduction processes.

STLK5 is more distantly related to this STE20-subfamily including SOK-1 and STLK2, STLK3 and STLK4. STLK5, may therefore mediate a signaling pathway that is distinct from the oxidative stress response pathway.

The high degree of sequence homology in the C-termini of SOK-1, STLK2, STLK3, STLK4, STLK5, and STLK6 raises the possibility that these novel STKs, like SOK-1, may be subject to autoinhibition through a conserved C-terminal motif.

Human ZC1, ZC2, ZC3 and ZC4

ZC1 is a good candidate for any disease in which tyrosine kinase, cytokine, or heterotrimeric G-protein coupled receptors have been implicated. The mouse homologue binds to NCK, and is recruited to activated PDGF (Su et al.,EMBO 16: 1279-1290, 1997). The Drosophila homolog has been shown to bind to TRAF2, implicating it in TNF-α signaling (Liu et al., (1999) Curr. Biol. 9:101-104, 1999)). While ZC1 does not contain the exact NCK- and TRAF2-binding domains, it is likely to bind to related proteins.

Of the ZC subfamily of STE20-related protein kinases, ZC1 has very broad over-expression in many tumor types, suggesting that it may be involved in cellular growth, transformation, or tumor progression. A truncated form of ZC1 containing only the C-terminal putative MEKK1-binding domain was found to reduce the number of foci generated by H-Ras-V12 in Rat Intestinal Epithelial cells (RIE-1). These data indicate that ZC1 may play a role in the ability for these cells to overcome contact inhibition and anchorage-dependent growth.

The ZC1 homolog, Misshapen (*msn*) in *Drosophila melanogaster* was cloned as a result of complementing a mutation in a developmental pathway required for dorsal

closure, a process involving changes in cell shape and position in the embryo (Treisman et al.Gene 186 119-125, 1997). A *D. melanogaster* homolog of the JNK1/JNK2 kinases from mammals was shown to function downstream of *msn* in the dorsal-closure signaling pathway (Su et al. Genes Dev. 12:2371-2380, 1998).

While ZC1 could be involved in multiple aspects of tumorigenesis, by analogy with *Drosophila*, the role of misshapen in dorsal closure suggests a critical role in the regulation of the cytoskeleton for the processes of cell attachment, cell movement and perhaps migration.

The association of the ZC1 family members *msn* and NIK with TRAF2 may indicate a role for this kinase in cell survival and/or in apoptosis. The ZC1 family contains a highly conserved domain that in the mouse homolog, NIK, has been shown to bind to MEKK1 (Mitogen-activated/ Extracellular-regulated Kinase Kinase 1) (Su et al., (1997) EMBO 16(6): 1279-90). MEKK1 is involved in cell survival and/or apoptosis in several systems (Schlesinger et al., Front. Biosci.3:D1181-6, 1998). Depending on the context, MEKK1 appears to be upstream of either the ERK1/MAPK or the JNK/SAPK pathway [Schlesinger et al., (1998 Front. Biosci. 3:D1181-6). Three homologues of ZC1: murine NIK (NCK-interacting kinase)(Su et al.EMBO 16:1279-90, 1997), *Drosophila msn* (Liu et al.Curr. Biol. 9:101-104, 1999) and human HGK (HPK/GCK-like kinase)(Yao et al., J. Biol. Chem. 274:2118-25, 1999) have all been shown to activate the JNK pathway when over-expressed in 293T cells.

ZC1 shares a high degree of homology with these other family members in both the kinase domain and the "MEKK"-binding domains, yet it differs in the intervening region, which contains several putative binding domains for upstream signaling adapter molecules (e.g. NCK, TRAF2). Unlike the

other family members, ZC1 does not appear to activate the JNK pathway in 293T cells as seen by its ability to induce expression of either a JUN or ATF2-driven luciferase gene. Upon co-transfection into these cells with HA-tagged JNK, modest activation of JNK was detected. ZC1 also modestly activated co-transfected ERK1. Both the ERK and the JNK activation were very slight compared with the positive controls in the assay (activated forms of MEK1 and MEKK1, respectively). In both cases, activation required the full-length kinase. While the kinase domain alone is up to 5x more active in autophosphorylation and in phosphorylation of MBP, it does not lead to activation of these potential downstream kinases. Based on the strong sequence homology of ZC1 with the other family members, it is very likely that ZC1 will be important for either JNK or ERK activation once the proper context is found.

ZC1 profoundly inhibits ERK1 kinase expression in co-transfection assays. This effect is dependent on ZC1 kinase activity, occurring with the wild-type and the kinase domain alone, but not with the kinase-dead mutant even though all three forms of ZC1 are expressed at similar levels. This may suggest a role for this kinase in transcriptional or post-transcriptional regulation.

ZC1 may be an important component in the signaling pathways mediated by the co-stimulatory receptor CD28 in T cells and/or by the pro-inflammatory cytokine TNFα, since co-transfection of the wild-type ZC1 activated the RE/AP-luciferase and NFκB-luciferase reporter genes. While our data showed that ZC1 strongly activates NFκB in T-cells, no activation of NFκB driven luciferase was detectable in NIH 3T3 cells. A recent paper (J. Biol. Chem. 274:2118-25; 1999.) has shown that a human ZC1 splicing isoform, HGK, is involved in the TNFα-signaling pathways.

Given the importance of T cell activation in autoimmunity and transplantation, as well as the key role that TNFα plays in inflammatory diseases, it is possible that ZC1 could be a therapeutic target for immunological diseases which include but are not limited to: rheumatoid arthritus, chronic inflammatory bowel diseases (ie Crohn's disease), chronic inflammatory pelvic disease, multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis, and autoimmunity as well as organ transplantation and cardiovascular diseases.

ZC1 appears to be the human orthologue of murine NIK and possibly an orthologue of a *C. elegans* STE20-subfamily kinase encoded by the ZC504.4 cosmid.

Murine NIK is a 140,000 daltons kinase that is most highly expressed in brain and heart. NIK interacts with the SH3 domains of the adaptor molecule Nck through its proline-rich regions found in the C-terminal extra-catalytic region. The specific regions that mediate this interaction are two PxxP motifs that are nearly uniformly conserved between NIK, ZC1,2,3 and the *C. elegans* STE20 ZC504.4 kinase. In addition, NIK binds MEKK1 through its 719 amino acid C-terminal (Su, Y-C. *et al.* (1997) EMBO J. 16, 1279-1290). MEKK1 is a membrane-associated kinase responsible for activating MKK4 (also known as SEK1), which in turn activates SAPK (Yan, M *et al.* (1994) Nature, 372, 798-800). NIK may function as a kinase that links growth factor activated pathways and the stress-response pathway mediated by SAPKs. According to this hypothesis, activation of growth factor receptors leads to receptor tyrosine phosphorylation, Nck binding to the phosphorylated tyrosines via its SH2 domain, NIK redistribution to a membrane compartment via binding to the SH3 domain of Nck, and juxtaposition to the membrane-associated MEKK1. The NIK-

MEKK1 interaction would, in this fashion, turn on the SAPK pathway in response to growth factor stimulation (Su, Y-C. *et al.* (1997) EMBO J. 16, 1279-1290).

Given the high homology between ZC1, ZC2, ZC3, and ZC4 STKs and NIK, it is conceivable that these kinases may each function to connect growth factor- and stress-activated signaling pathways. The heterogeneity that the ZC kinases exhibit within their putative SH3-binding domain could provide signaling specificity in terms of the nature of the adaptor molecule that they bind. The high level of sequence conservation in the C-termini of the ZC1, ZC2 and ZC3 strongly suggests that these human kinases, like murine NIK, also may bind to MEKK1 and activate SAPKs. The ZC kinases also display strong homology at their C-termini to protein domains that bind small GTPase proteins such as Rab, Rho and Rac. For example, the C-termini of ZC1 is 36.2% identical to citron, a murine Rho-binding protein, and 23.1% identical to the rab-binding region of GC kinase. This suggests that, in addition to adaptor molecules, small GTPase proteins may also mediate membrane association and activation of the ZC kinases. The presence of a potential coiled-coil region located immediately C-terminal to the catalytic region strongly suggests that the ZC kinases may also be subject to regulation via homo or heterodimerization events.

The *C. elegans* STE20 ZC504.4 kinase is the product of the mig-15 gene. The product of this gene has been implicated in several developmental processes such as epidermal development, Q neuroblast migrations and muscle arm targeting in the developing worm (Zhu, X. and Hedgecock E. (1997) Worm Breeder's Gazette 14, 76). The high level of sequence conservation between the ZC kinases and the ZC504.4 *C. elegans* kinase will make *C. elegans* a valuable model

organism to study, through epistatic analysis, the signaling properties of the human ZC kinases.

Human KHS2

KHS1 (kinase homologous to SPS1/STE20) is a 100,000 dalton cytoplasmic STK that is expressed ubiquitously. KHS1 has been implicated in the mechanism of SAPK activation in response to inflammatory cytokines such as TNFα as well as to ultraviolight light, which also uses the TNF signaling pathway. TNFα binding to its receptors (TNFR1 and TNFR2) results in the sequential association with the receptor C-tail of multiple signaling molecules including TNFR1-associated death domain protein (TRADD), Fas-associated death domain protein (FADD or MORT1), TNFR-associated factor 2 (TRAF2), and the STK RIP (receptor interacting protein). The TRADD-TRAF2 interaction is mediated by a conserved region present at the C-terminus of TRAF2, the TRAF domain. Activation of the NFκB and SAPK pathways is mediated by the ring finger motif present at the N-terminus of TRAF2 (Curr. Opinion in Cell. Biol. (1997) 9:247-251). KHS1 is activated by TNFα stimulation in a TRAF2-dependant manner and inhibition of KHS1 blocks TNFα-induced SAPK activation but not NFκB activation. The mechanism by which TRAF2 activates KHS1 is not known. Cotransfection of TRAF2- and KHS1-expressing constructs in 293T cells failed to reveal a direct association between these two molecules. KHS1 activates the SAPK pathway by a direct association with the constitutively active kinase MEKK1. MEKK1 subsequently activates SEK1, which in turn activates SAPK. Neither the MAPK nor the p38 kinase pathways are activated by KHS1 (Shi, C-S and Kehrl. J.H. (1997) J. Biol. Chem. 272, 32102-32107). In addition to its catalytic domain, downstream

signaling of KHS1 requires its conserved C-terminus (Diener, K. *et al* (1997) Proc. Natl. Acad. Sci. 94, 9687-9692).

GCK (germinal center kinase) is a constitutively active 97,000 dalton STK that is broadly expressed. GCK may participate in B-cell differentiation since its expression is localized to the germinal center within lymphoid follicles. GCK activates the SAPK pathway in response to TNFα via activation of SEK1. The upstream activators of GCK in response to cytokines as well as the immediate downstream target of this kinase are unknown. The C-terminus of GCK is sufficient to activate SEK1 (Pombo, C.M. *et al* (1995) Nature, 377, 750-754).

The murine orthologue of GCK, rab8ip (rab8-interacting protein), is a 97,000 dalton protein that fractionates with both the soluble cytoplasmic fraction as well as with a salt-sensitive fraction associated with the basolateral membrane of the trans-Golgi region in polarized MDCK epithelial cells. The C-terminus of rab8ip binds to rab8, a small GTP-binding protein required for vesicular transport from the Golgi apparatus (Ren, M. *et al.* (1996) Proc. Natl. Acad. Sci. 93, 5151-5155). In addition to inducing the transcriptional activation of cytokines like IL2 via SAPK, GCK may also promote the rab-dependent release of secretory proteins in response to TNFα (Buccione, R. *et al* (1995) Mol. Bio. Cell 6, 291).

HPK1 (hematopoietic protein kinase) is a constitutively active 90,000 dalton STK restricted to hematopoietic cells. HPK1 activates the SAPK pathway by directly binding to and activating MEKK1 (Hu, M. *et al* (1996) Genes and Dev. 10:2251-2264) as well as the ubiquitously expressed mixed-lineage kinase MLK-3 (Kiefer, F. *et al* (1996) EMBO J. 15:7013-7025). This function of HPK1 requires, in contrast to GCK, both its kinase domain as

well as its C-terminus. The upstream activators of HPK1 remain unknown. HPK1 also plays a key role as a mediator of transforming growth factor-β (TGFβ) signaling. HPK1 activates the TGFb-activated kinase (TAK), which in turn stimulates the SAPK pathway by phosphorylating SEK1 (Wang W. *et al* (1997) J. Biol. Chem. 272:22771-22775).

KHS2 is expressed in thymus, dendrocytes and monocytes. KHS2 could have a complementary function to that of KHS1 as a mediator of SAPK activation in the cellular response to inflammatory cytokines. KHS2 could have the potential to interact directly with TRAF2 since a STK with the predicted molecular weight of KHS2 (approximately 101,000 daltons) is found in the TNFR-TRAF2 complex upon TNFα stimulation (VanArsdale, T. and Ware, C.F. (1994) J. Immunol. 153, 3043-3050). The presence of a putative binding domain for Rab or a Rab-like molecule at the C-terminus of KHS2 indicates that KHS2, in addition to having a potential role in the TRAF2-dependant TNFα cytokine response, could also mediate signaling events that utilize small GTPase proteins. Alternatively, the binding of a small GTPase protein to the C-terminus of KHS2 may be required for its potential TRAF2-dependant signaling to a downstream kinase such as MEKK1.

Human GEK2, SULU1 and SULU3

A recent report (Y-W Qian et al., Science 282:1701-1704,1998) described xPlkk1 as the activator of Plx1 (the Xenopus Polo kinase). In Xenopus oocytes, the STK Plkk1 can phosphorylate and activate Plx1 STK (the mammalian Polo kinase or PLK). A dominant-negative (kinase-dead) form of xPlkk1 prevents Plx1 activation and delays germinal vesicle breakdown. Yet another unidentified kinase is probably responsible for xPlkk1 activation during mitosis.

The homology through the entire length of the xPlkk1 protein with GEK2 suggests that GEK2 might represent the human homologue for xPlkk1. Based on this, GEK2 might be upstream of PLK in mammalian cells. In addition, based on the phage display screen results using the SULU1 coiled-coil2 domain as bait, SULU1 might also interact in vivo with GEK2 and therefore regulate GEK2 (and/or SLK through the coiled-coil domain) activation leading to PLK activation and mitosis.

If such a cascade of events is required for mitosis in mammalian cells, interruption of this signaling cascade at any point might block mitosis and could be beneficial for cancer treatment.

A recently cloned STE20-subfamily kinase, rat TAO1, is most likely the rodent orthologue of human SULU3 (Hutchinson, M. *et al*. J. Biol. Chem 273:28625-28632, 1998). TAO1 activates MEK3, 4 and 6 in vitro, while in transfected cells it associates and activates only MEK3, resulting in phosphorylation and activation of p38. These results implicate TAO1 (SULU3) in the regulation of the p38 containing stress-responsive MAP kinase pathway.

Human SULU1 is weakly expressed in hematopoietic sources whereas SULU3 is found in B-cells and TH1-restricted T cells. These mammalian SULU STKs display strong homology to the *C. elegans* SULU kinase. The role that this kinase plays in nematode development is unknown. The strong sequence homology between the catalytic domain of mammalian SULU kinases and other STE20-subfamily kinases such as SOK-1 (human STE20) and KHS2 suggests that the mammalian kinases may participate in the stress-response pathway. The potential coiled-coil domains found at the C-terminus of the SULU kinases may play a role in the regulation of this kinase.

Murine LOK (lymphocyte-oriented kinase) is a constitutively activated STK of approximately 130,000 daltons that is predominantly expressed in spleen, thymus and bone marrow (Kuramochi, S. *et al* (1997) J. Biol. Chem. 272: 22679-22684) as well as in meiotic testicular and primordial germ cells. The LOK1 gene is located in chromosome 11 of the mouse near the *wr* locus, a region that is associated with reproductive and neurological defects (Yanagisawa, M. *et al* (1996) Mol. Reprod. and Dev. 45:411-420). LOK does not activate any of the known MAPK pathways (ERK, JNK and p38) nor the NFkB pathway. The upstream signaling elements of LOK as well as the extracellular stimuli that utilize this kinase to elicit a biological response are also unknown (Kuramochi, S. *et al* (1997) J. Biol. Chem. 272: 22679-22684).

Human GEK2 is highly related to murine LOK, but based on sequence divergence in the non-catalytic domain, it appears to be a distinct member of this STE20-subfamily. GEK2 may signal through a pathway that remains to be defined. The presence of potential coiled-coil regions at the C-terminus of GEK2 could play a key role in regulating the functions of this kinase.

Human PAK4 and PAK5

The p21 activated protein kinases (PAK) are a closely related subgroup of the STE20 family of serine/threonine kinases. Extensive genetic and biochemical analysis of the budding yeast STE20 has shown the critical role this serine/threonine kinase plays at the juncture of several important intracellular pathways required to appropriately respond to extracellular signals. STE20 links the transcriptional response by mediating the activation of the appropriate downstream MAPK pathway as well as coupling

changes in cellular morphology via its control of the actin cytoskeleton.

A hallmark of the PAK subgroup is their small G protein-binding domain (PBD) that confers G protein-dependent activation upon this group of kinases. Via the PBD, PAKs bind to activated small G proteins resulting in the derepression of the PAK's intrinsic kinase activity.

Until recently, there were three known PAK kinases: PAK1, a 68 kD protein whose expression is restricted expression to brain, muscle, and spleen; PAK2 (PAKI, PAK65), a 62 kD protein whose expression is ubiquitous; and PAK3, a 65kD protein whose expression is restricted to the brain. Similar to STE20, the mammalian PAKs (1,2, and 3) have been shown to respond to extracellular signals (growth factors, mitogens, cytokines and a variety of cellular stresses) (Bagrodia, *et al*. (1995). J. Biol. Chem. 270: 22731-22737; Zhang, S., *et al*. (1995). J. Biol. Chem. 270: 23934-23936, Frost, J. *et al*. (1998) J. Biol. Chem. 273: 28191-28198; Galisteo, M. *et al*. (1996) J. Biol. Chem. 271: 20997-21000), and are linked to TCR activation (Yablonski, D., *et al*. (1998) EMBO J. 17: 5647-5657), and heterotrimeric G protein-coupled receptors (Knaus, U. *et al*. (1995) Science 269: 221-223).

The PAKs were originally identified as effectors for members of the Rho family of small G proteins (such as Rac and Cdc42), hence their name, p21-activated kinases (PAK) (Manser *et al* Nature 367:40-46). The recruitment of the PAKs to the appropriate intracellular location is critical to their function. Attempts to elucidate the role played by PAKs in intracellular signaling and morphological changes is complicated due to the complex interactions by which they can be recruited by such factors as activated small G

proteins (rac, cdc42), adaptors (nck) and exchange proteins (PIX, Cool).

The adaptor molecule, Nck, is constitutively bound via its SH3 domain to the proline-rich motif in the N-terminal portion of PAK1. Binding of the Nck-PAK complex to activated growth factor receptors in response to growth factor stimulation provides a mechanism to link growth factor-stimulated and stress-response pathways (Galisteo, M. *et al.* (1996) J. Biol. Chem. 271:20997-21000).

The PBD found at the N-terminus of PAK1 is responsible for its high-affinity interaction with the GTP-bound forms of Cdc42 and Rac (Burbelo, P. *et al.* (1995) J. Biol. Chem. 270:29071-29074). The exact mechanism through which the small GTPases activate PAKs may involve, in part, association of the kinase with activated growth factor receptors through guanine nucleotide exchange factors (GEFs). GEFs activate small GTPases by catalyzing the formation of their GTP-bound state, thereby promoting their association with, and activation of, PAKs. The known mammalian PAK kinases, as well as *Drosophila* and *C. elegans* PAKs, all conserve an N-terminal extracatalytic motif responsible for a high-affinity interaction with the GEF, PIX. The PAK-Cdc42 interaction and subsequent PAKs occurs as a PIX/PAK complex (Manser, E. *et al.* (1998) Molecular Cell, 1, 183-192).

PAK signaling stimulated by heterotrimeric G proteins is mediated through the interaction between a short conserved amino acid region located at the C-terminus of PAK1 with the G-protein β-subunit (Leeuw, T. *et al.*(1998) Nature, 391: 191-195).

A variety of studies have indicated that the human PAKs are involved in mediating the activation of stress-activated protein kinase pathways (JNK and to lesser extent p38).

PAKs are also potential mediators in the crosstalk between the pathways regulated by the Rho family of small G proteins and the signaling pathways directly downstream of Ras leading to the activation of the ERK pathway (Bagrodia, *et al.* (1995). J. Biol. Chem. 270: 22731-22737; Zhang, S., *et al.* (1995). J. Biol. Chem. 270: 23934-23936; Brown, J., *et al.* (1996) Curr Biol. 6:598-60596; Frost, J., *et al.* (1996). Mol. Cell. Biol. 16: 3707-3713).

PAK1 has been implicated in phosphorylating a regulatory site in MEK1 that is necessary for MEK1's ability to interact with Raf1 (Frost, *et al.* (1997) EMBO J. 16:6426-6438). PAK3 has been shown to phosphorylate Raf1 on a site that is important for Raf1 activity (King, A., *et al.* (1998). Nature 396: 180-183).

PAKs play an important role in controlling morphological changes in cell shape mediated by the actin cytoskeleton. Such morphological changes are required for cellular functions ranging from cell division and proliferation to cell motility and vesicle transport. PAK activity has been implicated in the localized assembly (leading edge) and disassembly (retracting edge) of focal adhesions necessary for cell motility (Frost J. *et al* (1998) J. Biol. Chem. 273:28191-28198).

PAK2 may have a role in the morphological changes induced during apoptosis (Membrane and morphological changes in apoptotic cells regulated by caspase-mediated activation of PAK2. (Rudel, T. (1997) Science. 276:1571-4)), and PAK1 may be important in preventing apoptosis (Faure S, *et al.* (1997) EMBO J. (1997) 16:5550-61). In addition to overcoming mitogen- and anchorage-independent growth, tumor cells need to escape the programmed cell death that accompanies deregulated cell growth. Thus, inhibition of PAKs may be effective in triggering apoptosis in tumors.

A direct requirement for PAKs in the transformation of mammalian cells has been shown for PAK1 and PAK2. Kinase-dead alleles of PAK1 block ras transformation of RAT1 and Schwann cells (Tang, Y., *et al.* (1997) Mol. Cell. Biol. 17, 4454-4464). Dominant-negative alleles of PAK2 have been shown to interfere with ras-mediated transformation of mammalian cells (Osada, S., (1997) FEBS Lett 404:227-233)

Mutations in PAK3 have been implicated in nonsyndromic X-linked mental retardation suggesting a role for PAK3 in cognitive function (Allen, K. *et al.* (1998) Nat. Genet. 20: 25-30). PAK1 has been implicated in neurite outgrowth in PC12 cells (Daniels, R. *et al.* (1998) EMBO J. 17: 754-764; Nikolic, M. *et al.* (1998) Nature 395:194-198).

Finally, PAK-like STKs may also play a role in AIDS pathogenesis since the myristoylated 27kD membrane-associated HIV Nef gene product directly interacts with and activates these kinases via cdc42 and Rac. The Nef-mediated activation of PAK-like STKs correlates with the induction of high viral titers and the development of AIDS in infected hosts (Cullen, B. R. (1996) Curr. Biol. 6:1557-1559).

Our results show that PAK4 is expressed in thymus, dendrocytes, mast cells, monocytes, as well as in T cells (TH2-restricted cells and MOLT4) and the B cell line RPMI. PAK5 is found in mast cells and in the T cell line MOLT4. These data suggest potential roles for PAK4 and PAK5 in the immune system.

PAK4 and PAK5 share with the known PAKs a potential cdc42-binding motif at their N-termini. Both PAK4 and PAK5 display sequence homology in their C-termini to a motif responsible for an interaction between PAK1 and the β-subunit of heterotrimic G-proteins (amino acid residues 665-676 in PAK 4, and amino acid residues 386-398 in PAK5). Consequently, PAK4, and possibly PAK5, could mediate

signaling events originating from growth factors as well as from ligands that stimulate G-protein-linked receptors.

PAK4 conserves a leucine (leu 44), that when mutated to a phenylalanine renders the kinase activity of human PAK1 constitutively active, bypassing its cdc42-binding requirement for activation (Brown J. *et al* (1996) Current Biol. 6:598-605). PAK5 contains an isoleucine at the equivalent position. Therefore, the mechanism by which cdc42 potentially activates human PAK1, PAK4, and possibly PAK5, may be very similar.

PAK4 and PAK5 however, lack the PIX-binding motif, and consequently cdc42-activating GEFs other than PIX (for example Dbl and Cool) must be responsible for the activation of these kinases. Alternatively, PAK4 and PAK5 may be activated by another GTPase, such as Rac1 which uses the Tiam1 GEF for its activation to the GTP-bound state.

PAK4 and PAK5 also lack the PxxP motif responsible for the Nck-PAK1 association. Between the PBD or cdc42-binding N-terminal motifs and the putative GEF-binding regions, PAK4 and PAK5 have long insertions (185 and 123 amino acids for PAK4 and PAK5, respectively) relative to PAK1. This region probably confers different binding characteristics to adaptor molecules and/or GEFs from those exhibited by known mammalian PAKs.

PAKs have been shown to be upstream in pathways leading to activation of both the JNK (Bagrodia, S., *et al.* (1995) J. Biol. Chem. 270: 22731-22737) and ERK kinase pathways (Brown, J., *et al.* (1996). Curr Biol. 6:598-605). PAK1 was shown to synergize with ras in activation of the ERK pathway through phosphorylation of MEK1 (Frost, J. *et al.* (1997). EMBO J. 16:6426-6438). Our data shows that MEK1 serves as an *in vitro* substrate for PAK4, suggesting a potential role

for PAK4 in the activation of the ERK pathway and mitogenesis.

PAK5 may also have a mitogenic role, and be linked to cancer, based on its expression profile (elevated RNA and protein levels in a wide variety of tumor cell lines), its interaction with cdc42 via its PBD, and the ability of a kinase-dead allele (Lys350, 351 Ala) to block ras transformation of NIH3T3 cells. Thus, a screen for small molecule inhibitors of PAK5 kinase activity may yield compounds with therapeutic potential for intervention in cancer derived from a wide variety of tissue types.

PAK4 and PAK5 may also play a role in HIV pathogenesis as potential mediators of Nef signaling, since none of the known PAKs correspond to the PAK-like kinase shown to interact with, and be activated by, the HIV nef protein (Lu, X. *et al.* (1996) Current Biology 6:1677-1684)

The 3' untranslated region of PAK4 contains a CA repeat that is prone to undergo expansion. CA dinucleotide repeat instability has been associated with disease (Toren, M.Z. *et al* (1998) Am. J. Hematol. 57: 148-152), and expansion of such repeat in the 3' untranslated region of PAK4 could implicate this kinase in as yet unknown pathologies.

<u>Clinical applications</u>

<u>Human STLK2, STLK3, STLK4, STLK5, STLK6, and STLK7</u>

STLK3, STLK5, STLK6 and STLK7, as well as other homologues of the STLK subfamily of STE20 protein kinases such as STLK4, may play an important role as mediators of the immune response. Thus, they are targets for the development of specific small molecule inhibitors to treat immunological diseases, including, but not limited to, rheumatoid arthritis, chronic inflammatory bowel diseases (e.g. Crohn's disease), chronic inflammatory pelvic disease,

multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis and autoimmunity, as well as in organ transplantation. Other diseases include cardiovascular diseases.

The human STLKs may also play an important role in cell growth regulation. Thus, they are targets for developing small molecule kinase inhibitors for the treatment of cancer and metastases. STLK5 maps to a chromosomal region frequently amplified in a variety of tumors including those from non-small cell lung cancer, breast cancer and peripheral nerve tumors. This suggests that STLK5 could play a role in the development, maintenance, or progression of human tumors.

The potential role of human STLKs 2,3, and 4 in mediating oxidative stress strongly suggests that drugs targeting these kinases could prove useful in the treatment of myocardial infarction, arrhythmia and other cardiomyopathies, stroke, renal failure, oxidative stress-related neurodegenerative disorders such amyotrophic lateral sclerosis, Parkinson's disease and Leigh syndrome, a necrotizing mitochondrial encephalopathy, as well.

Human ZC1, ZC2, ZC3, and ZC4

ZC1 may be a component of the CD28-signaling pathway and therefore important in T cell activation. As such, ZC1 as well as other ZC subfamily kinases, are targets for the development of specific small molecule inhibitors to treat immunological diseases, including, but not limited to, rheumatoid arthritis, chronic inflammatory bowel diseases (e.g. Crohn's disease), chronic inflammatory pelvic disease, multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis and autoimmunity, as well as organ

transplantation. Other diseases include cardiovascular diseases.

ZC1 and ZC2 are also implicated in cell growth regulation. Thus, ZC subfamily kinases are targets for developing small molecule inhibitors for the treatment of cancer and metastases. ZC2 maps to a chromosomal region frequently amplified in a variety of tumors including those from non-small cell lung cancer, small cell lung cancer, and cervical cancer. This suggests that ZC2 could play a role in the development, maintenance, or progression of human tumors.

The role of human ZC1, ZC2, ZC3, and ZC4 in the inflammatory and stress-response pathways, strongly suggests that drugs targeting these kinases could have strong immunosuppressive actions. These drugs can prove valuable for the treatment of rheumatoid arthritis, artherosclerosis, autoimmune disorders and organ transplantation among others. At least one very important class of immunosuppresants, corticosteroids, functions by blocking SAPK activation at an as yet undefined site on this pathway (Swantek, J.L. *et al* (1997) Mol. Cell. Biol. (1997) 6274-6282). Other immunosuppresive drugs like the pyridinyl imidazoles specifically target the p38 kinases (Kumar, S. *et al* (1997) Biochem. Biophys. Res. Commun. 235: 533-528). Drug targeting of the MAPK and p38 pathways could lead to the development of novel immunosuppresants.

<u>Human SULU and GEK</u>

The potential role of these novel STE20-related protein kinases in the control of mitosis strongly suggests that agents that specifically inhibit these kinases could be useful for cancer and metastases treatment.

The close homology of human STLK5, GEK2, SULU1 and SULU3 to STE20-subfamily kinases involved in the stress and oxidative response pathway strongly suggests that drugs targeting these kinases may also be useful as immunosuppressants as well as to treat ischemic disorders.

Human KHS2

The role of human KHS2 in the inflammatory and stress-response pathways, strongly suggests that drugs targeting this and related kinases could have strong immunosuppressive actions. These drugs can prove valuable for the treatment of rheumatoid arthritis, artherosclerosis, autoimmune disorders and organ transplantation among others. At least one very important class of immunosuppresants, corticosteroids, functions by blocking SAPK activation at an as yet undefined site on this pathway (Swantek, J.L. *et al* (1997) Mol. Cell. Biol. (1997) 6274-6282). Other immunosuppresive drugs like the pyridinyl imidazoles specifically target the p38 kinases (Kumar, S. *et al* (1997) Biochem. Biophys. Res. Commun. 235: 533-528). Drug targeting of the MAPK and p38 pathways could lead to the development of novel immunosuppressants.

Human PAK family

PAK5 has a role in cancer based on its expression profile (elevated RNA and protein levels in wide variety of tumor lines), its interaction with Cdc42 via its PBD, and the ability of the kinase-dead allele of PAK5 (Lys350, 351Ala) to block ras transformation of NIH3T3 cells. Thus, a screen for small molecule inhibitors of PAK5 kinase activity may yield compounds with therapeutic potential for intervention in cancers and metastases derived from a wide range of tissue types.

PAK5 maps to a chromosomal region frequently amplified in a variety of tumors including those from non-small cell lung cancer, and small cell lung cancer. These findings suggest that PAK5 could play a role in the development, maintenance, or progression of human tumors and/or metastases.

The role of human PAK4, and PAK5 in the inflammatory and stress-response pathways also strongly suggests that drugs targeting these kinases could have strong immunosuppressive actions. These drugs can prove valuable for the treatment of rheumatoid arthritis, artherosclerosis, autoimmune disorders and organ transplantation among others. At least one very important class of immunosuppresants, corticosteroids, functions by blocking SAPK activation at an as yet undefined site on this pathway (Swantek, J.L. *et al* (1997) Mol. Cell. Biol. (1997) 6274-6282). Other immunosuppresive drugs like the pyridinyl imidazoles specifically target the p38 kinases (Kumar, S. *et al* (1997) Biochem. Biophys. Res. Commun. 235: 533-528). Drug targeting of the MAPK and p38 pathways could lead to the development of novel immunosuppresants. In addition, drugs targeting PAK4 or PAK5 could prove useful as immunosuppresants as well as in AIDS treatment.

<u>VIII</u>. <u>Transgenic Animals</u>.

A variety of methods are available for the production of transgenic animals associated with this invention. DNA can be injected into the pronucleus of a fertilized egg before fusion of the male and female pronuclei, or injected into the nucleus of an embryonic cell (*e.g.*, the nucleus of a two-cell embryo) following the initiation of cell division (Brinster *et al.*, Proc. Nat. Acad. Sci. USA 82: 4438-4442, 1985). Embryos can be infected with viruses, especially

retroviruses, modified to carry inorganic-ion receptor nucleotide sequences of the invention.

Pluripotent stem cells derived from the inner cell mass of the embryo and stabilized in culture can be manipulated in culture to incorporate nucleotide sequences of the invention. A transgenic animal can be produced from such cells through implantation into a blastocyst that is implanted into a foster mother and allowed to come to term. Animals suitable for transgenic experiments can be obtained from standard commercial sources such as Charles River (Wilmington, MA), Taconic (Germantown, NY), Harlan Sprague Dawley (Indianapolis, IN), etc.

The procedures for manipulation of the rodent embryo and for microinjection of DNA into the pronucleus of the zygote are well known to those of ordinary skill in the art (Hogan *et al.*, supra). Microinjection procedures for fish, amphibian eggs and birds are detailed in Houdebine and Chourrout (Experientia 47: 897-905, 1991). Other procedures for introduction of DNA into tissues of animals are described in U.S. Patent No., 4,945,050 (Sandford *et al.*, July 30, 1990).

By way of example only, to prepare a transgenic mouse, female mice are induced to superovulate. Females are placed with males, and the mated females are sacrificed by CO_2 asphyxiation or cervical dislocation and embryos are recovered from excised oviducts. Surrounding cumulus cells are removed. Pronuclear embryos are then washed and stored until the time of injection. Randomly cycling adult female mice are paired with vasectomized males. Recipient females are mated at the same time as donor females. Embryos then are transferred surgically. The procedure for generating transgenic rats is similar to that of mice (Hammer *et al.*, Cell 63:1099-1112, 1990).

Methods for the culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection also are well known to those of ordinary skill in the art (Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E.J. Robertson, ed., IRL Press, 1987).

In cases involving random gene integration, a clone containing the sequence(s) of the invention is co-transfected with a gene encoding resistance. Alternatively, the gene encoding neomycin resistance is physically linked to the sequence(s) of the invention.. Transfection and isolation of desired clones are carried out by any one of several methods well known to those of ordinary skill in the art (E.J. Robertson, supra).

DNA molecules introduced into ES cells can also be integrated into the chromosome through the process of homologous recombination (Capecchi, Science 244: 1288-1292, 1989). Methods for positive selection of the recombination event (*i.e.*, neo resistance) and dual positive-negative selection (*i.e.*, neo resistance and gancyclovir resistance) and the subsequent identification of the desired clones by PCR have been described by Capecchi, supra and Joyner *et al.* (Nature 338: 153-156, 1989), the teachings of which are incorporated herein in their entirety including any drawings. The final phase of the procedure is to inject targeted ES cells into blastocysts and to transfer the blastocysts into pseudopregnant females. The resulting chimeric animals are bred and the offspring are analyzed by Southern blotting to identify individuals that carry the transgene. Procedures for the production of non-rodent mammals and other animals have been discussed by others (Houdebine and Chourrout, supra; Pursel *et al.*, Science

244:1281-1288, 1989; and Simms *et al.*, Bio/Technology 6:179-183, 1988).

Thus, the invention provides transgenic, nonhuman mammals containing a transgene encoding a kinase of the invention or a gene effecting the expression of the kinase. Such transgenic nonhuman mammals are particularly useful as an *in vivo* test system for studying the effects of introduction of a kinase, or regulating the expression of a kinase (*i.e.*, through the introduction of additional genes, antisense nucleic acids, or ribozymes).

A "transgenic animal" is an animal having cells that contain DNA which has been artificially inserted into a cell, which DNA becomes part of the genome of the animal which develops from that cell. Preferred transgenic animals are primates, mice, rats, cows, pigs, horses, goats, sheep, dogs and cats. The transgenic DNA may encode human STE20-related kinases. Native expression in an animal may be reduced by providing an amount of anti-sense RNA or DNA effective to reduce expression of the receptor.

IX. Gene Therapy

STE20-related kinases or their genetic sequences will also be useful in gene therapy (reviewed in Miller, Nature 357:455-460, 1992). Miller states that advances have resulted in practical approaches to human gene therapy that have demonstrated positive initial results. The basic science of gene therapy is described in Mulligan (Science 260:926-931, 1993).

In one preferred embodiment, an expression vector containing STE20-related kinase coding sequence is inserted into cells, the cells are grown *in vitro* and then infused in large numbers into patients. In another preferred embodiment, a DNA segment containing a promoter of choice (for

example a strong promoter) is transferred into cells containing an endogenous gene encoding kinases of the invention in such a manner that the promoter segment enhances expression of the endogenous kinase gene (for example, the promoter segment is transferred to the cell such that it becomes directly linked to the endogenous kinase gene).

The gene therapy may involve the use of an adenovirus containing kinase cDNA targeted to a tumor, systemic kinase increase by implantation of engineered cells, injection with kinase-encoding virus, or injection of naked kinase DNA into appropriate tissues.

Target cell populations may be modified by introducing altered forms of one or more components of the protein complexes in order to modulate the activity of such complexes. For example, by reducing or inhibiting a complex component activity within target cells, an abnormal signal transduction event(s) leading to a condition may be decreased, inhibited, or reversed. Deletion or missense mutants of a component, that retain the ability to interact with other components of the protein complexes but cannot function in signal transduction may be used to inhibit an abnormal, deleterious signal transduction event.

Expression vectors derived from viruses such as retroviruses, vaccinia virus, adenovirus, adeno-associated virus, herpes viruses, several RNA viruses, or bovine papilloma virus, may be used for delivery of nucleotide sequences (*e.g.*, cDNA) encoding recombinant kinase of the invention protein into the targeted cell population (*e.g.*, tumor cells). Methods which are well known to those skilled in the art can be used to construct recombinant viral vectors containing coding sequences (Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor

Laboratory, N.Y., 1989; Ausubel et al., Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, N.Y., 1989). Alternatively, recombinant nucleic acid molecules encoding protein sequences can be used as naked DNA or in a reconstituted system *e.g.*, liposomes or other lipid systems for delivery to target cells (*e.g.*, Felgner *et al.*, Nature 337:387-8, 1989). Several other methods for the direct transfer of plasmid DNA into cells exist for use in human gene therapy and involve targeting the DNA to receptors on cells by complexing the plasmid DNA to proteins (Miller, supra).

In its simplest form, gene transfer can be performed by simply injecting minute amounts of DNA into the nucleus of a cell, through a process of microinjection (Capecchi, Cell 22:479-88, 1980). Once recombinant genes are introduced into a cell, they can be recognized by the cell's normal mechanisms for transcription and translation, and a gene product will be expressed. Other methods have also been attempted for introducing DNA into larger numbers of cells. These methods include: transfection, wherein DNA is precipitated with $CaPO_4$ and taken into cells by pinocytosis (Chen *et al.*, Mol. Cell Biol. 7:2745-52, 1987); electroporation, wherein cells are exposed to large voltage pulses to introduce holes into the membrane (Chu *et al.*, Nucleic Acids Res. 15:1311-26, 1987); lipofection/liposome fusion, wherein DNA is packaged into lipophilic vesicles which fuse with a target cell (Felgner *et al.*, Proc. Natl. Acad. Sci. USA. 84:7413-7417, 1987); and particle bombardment using DNA bound to small projectiles (Yang *et al.*, Proc. Natl. Acad. Sci. 87:9568-9572, 1990). Another method for introducing DNA into cells is to couple the DNA to chemically modified proteins.

It has also been shown that adenovirus proteins are capable of destabilizing endosomes and enhancing the uptake of DNA into cells. The admixture of adenovirus to solutions containing DNA complexes, or the binding of DNA to polylysine covalently attached to adenovirus using protein crosslinking agents substantially improves the uptake and expression of the recombinant gene (Curiel *et al.*, Am. J. Respir. Cell. Mol. Biol., 6:247-52, 1992).

As used herein "gene transfer" means the process of introducing a foreign nucleic acid molecule into a cell. Gene transfer is commonly performed to enable the expression of a particular product encoded by the gene. The product may include a protein, polypeptide, anti-sense DNA or RNA, or enzymatically active RNA. Gene transfer can be performed in cultured cells or by direct administration into animals. Generally gene transfer involves the process of nucleic acid contact with a target cell by non-specific or receptor mediated interactions, uptake of nucleic acid into the cell through the membrane or by endocytosis, and release of nucleic acid into the cytoplasm from the plasma membrane or endosome. Expression may require, in addition, movement of the nucleic acid into the nucleus of the cell and binding to appropriate nuclear factors for transcription.

As used herein "gene therapy" is a form of gene transfer and is included within the definition of gene transfer as used herein and specifically refers to gene transfer to express a therapeutic product from a cell *in vivo* or *in vitro*. Gene transfer can be performed *ex vivo* on cells which are then transplanted into a patient, or can be performed by direct administration of the nucleic acid or nucleic acid-protein complex into the patient.

In another preferred embodiment, a vector having nucleic acid sequences encoding a STE20-related kinase

polypeptide is provided in which the nucleic acid sequence is expressed only in specific tissue. Methods of achieving tissue-specific gene expression are set forth in International Publication No. WO 93/09236, filed November 3, 1992 and published May 13, 1993.

In all of the preceding vectors set forth above, a further aspect of the invention is that the nucleic acid sequence contained in the vector may include additions, deletions or modifications to some or all of the sequence of the nucleic acid, as defined above.

In another preferred embodiment, a method of gene replacement is set forth. "Gene replacement" as used herein means supplying a nucleic acid sequence which is capable of being expressed *in vivo* in an animal and thereby providing or augmenting the function of an endogenous gene which is missing or defective in the animal.

X. Administration of Substances

Methods of determining the dosages of compounds to be administered to a patient and modes of administering compounds to an organism are disclosed in U.S. Application Serial No. 08/702,282, filed August 23, 1996 and International patent publication number WO 96/22976, published August 1 1996, both of which are incorporated herein by reference in their entirety, including any drawings, figures, or tables. Those skilled in the art will appreciate that such descriptions are applicable to the present invention and can be easily adapted to it.

The proper dosage depends on various factors such as the type of disease being treated, the particular composition being used, and the size and physiological condition of the patient. Therapeutically effective doses for the compounds described herein can be estimated initially from

cell culture and animal models. For example, a dose can be formulated in animal models to achieve a circulating concentration range that initially takes into account the IC_{50} as determined in cell culture assays. The animal model data can be used to more accurately determine useful doses in humans.

Plasma half-life and biodistribution of the drug and metabolites in the plasma, tumors, and major organs can be also be determined to facilitate the selection of drugs most appropriate to inhibit a disorder. Such measurements can be carried out. For example, HPLC analysis can be performed on the plasma of animals treated with the drug and the location of radiolabeled compounds can be determined using detection methods such as X-ray, CAT scan, and MRI. Compounds that show potent inhibitory activity in the screening assays, but have poor pharmacokinetic characteristics, can be optimized by altering the chemical structure and retesting. In this regard, compounds displaying good pharmacokinetic characteristics can be used as a model.

Toxicity studies can also be carried out by measuring the blood cell composition. For example, toxicity studies can be carried out in a suitable animal model as follows: 1) the compound is administered to mice (an untreated control mouse should also be used); 2) blood samples are periodically obtained via the tail vein from one mouse in each treatment group; and 3) the samples are analyzed for red and white blood cell counts, blood cell composition, and the percent of lymphocytes versus polymorphonuclear cells. A comparison of results for each dosing regime with the controls indicates if toxicity is present.

At the termination of each toxicity study, further studies can be carried out by sacrificing the animals (preferably, in accordance with the American Veterinary

Medical Association guidelines Report of the American Veterinary Medical Assoc. Panel on Euthanasia, *Journal of American Veterinary Medical Assoc., 202*:229-249, 1993). Representative animals from each treatment group can then be examined by gross necropsy for immediate evidence of metastasis, unusual illness, or toxicity. Gross abnormalities in tissue are noted, and tissues are examined histologically. Compounds causing a reduction in body weight or blood components are less preferred, as are compounds having an adverse effect on major organs. In general, the greater the adverse effect the less preferred the compound.

For the treatment of cancers the expected daily dose of a hydrophobic pharmaceutical agent is between 1 to 500 mg/day, preferably 1 to 250 mg/day, and most preferably 1 to 50 mg/day. Drugs can be delivered less frequently provided plasma levels of the active moiety are sufficient to maintain therapeutic effectiveness.

Plasma levels should reflect the potency of the drug. Generally, the more potent the compound the lower the plasma levels necessary to achieve efficacy.

EXAMPLES

The examples below are not limiting and are merely representative of various aspects and features of the present invention. The examples below demonstrate the isolation and characterization of the STE20-related kinases of the invention.

EXAMPLE 1: Isolation of cDNAs Encoding Mammalian STE20-related Protein Kinases

Materials and Methods

Identification of novel clones

Total RNAs were isolated using the Guanidine Salts/Phenol extraction protocol of Chomczynski and Sacchi (P. Chomczynski and N. Sacchi, Anal. Biochem. 162, 156 (1987)) from primary human tumors, normal and tumor cell lines, normal human tissues, and sorted human hematopoietic cells. These RNAs were used to generate single-stranded cDNA using the Superscript Preamplification System (GIBCO BRL, Gaithersburg, MD; Gerard, GF *et al.* (1989), FOCUS 11, 66) under conditions recommended by the manufacturer. A typical reaction used 10 µg total RNA with 1.5 µg oligo(dT)$_{12-18}$ in a reaction volume of 60 µL. The product was treated with RNaseH and diluted to 100 µL with H_2O. For subsequent PCR amplification, 1-4 µL of this sscDNA was used in each reaction.

Degenerate oligonucleotides were synthesized on an Applied Biosystems 3948 DNA synthesizer using established phosphoramidite chemistry, precipitated with ethanol and used unpurified for PCR. The sequence of some of the degenerate oligonucleotide primers and the amino acid motif they encode is as follows:

TRK1	5'-CTGAATTCGGNGCNTTYGGNAARGT-3'	GAFGKV (sense)
TRK4	5'-GCTGGATCCYTCNGGNGGCATCCA-3'	WMPPE (antisense)
ROS1	5'-GCNTTYGGNGARGTNTAYGARGG-3'	AFGEVYEG (sense)
CCK4b	5'-GCTGGATCCYTCNGGNSWCATCCA-3'	WMSPE (antisense)
CCK4c	5'-GAGTTYGGNGARGTNTTYYTNGC-3'	EFGEVYEG (sense)

These primers were derived from the sense and antisense strands of conserved motifs within the catalytic domain of several protein kinases. Degenerate nucleotide residue

designations are: N = A, C, G, or T; R = A or G; Y = C or T; H = A, C or T not G; D = A, G or T not C; S = C or G; and W = A or T.

PCR reactions were performed using degenerate primers applied to multiple single-stranded cDNAs. The primers were added at a final concentration of 5 µM each to a mixture containing 10 mM TrisHCl, pH 8.3, 50 mM KCl, 1.5 mM $MgCl_2$, 200 µM each deoxynucleoside triphosphate, 0.001% gelatin, 1.5 U AmpliTaq DNA Polymerase (Perkin-Elmer/Cetus), and 1-4 µL cDNA. Following 3 min denaturation at 95 °C, the cycling conditions were 94 °C for 30 s, 50 °C for 1 min, and 72 °C for 1 min 45 s for 35 cycles. PCR fragments migrating between 300-350 bp were isolated from 2% agarose gels using the GeneClean Kit (Bio101), and T-A cloned into the pCRII vector (Invitrogen Corp. U.S.A.) according to the manufacturer's protocol.

Colonies were selected for mini plasmid DNA-preparations using Qiagen columns and the plasmid DNA was sequenced using a cycle sequencing dye-terminator kit with AmpliTaq DNA Polymerase, FS (ABI, Foster City, CA). Sequencing reaction products were run on an ABI Prism 377 DNA Sequencer, and analyzed using the BLAST alignment algorithm (Altschul, S.F. *et al.*, J.Mol.Biol. 215: 403-10).

Additional PCR strategies were employed to connect various PCR fragments or ESTs using exact or near exact oligonucleotide primers as detailed in the results section for each cDNA. PCR conditions were as described above except the annealing temperatures were calculated for each oligo pair using the formula: Tm = 4(G+C)+2(A+T).

Isolation of cDNA clones:

Human cDNA libraries were probed with PCR or EST fragments corresponding to STE20-related genes. Probes were

^{32}P-labeled by random priming and used at $2x10^6$ cpm/mL following standard techniques for library screening. Pre-hybridization (3 h) and hybridization (overnight) were conducted at 42 °C in 5X SSC, 5X Denhart's solution, 2.5% dextran sulfate, 50 mM $Na_2PO_4/NaHPO_4$, pH 7.0, 50% formamide with 100 mg/mL denatured salmon sperm DNA. Stringent washes were performed at 65 °C in 0.1X SSC and 0.1% SDS. DNA sequencing was carried out on both strands using a cycle sequencing dye-terminator kit with AmpliTaq DNA Polymerase, FS (ABI, Foster City, CA). Sequencing reaction products were run on an ABI Prism 377 DNA Sequencer.

Makegene Bioinformatics EST assembler

The EST reports were downloaded from ncbi (www.ncbi.nlm.nih.gov). After uncompressing the files, the program 'report2est' was scripted to extract the following information: 1) EST names, 2) GenBank Accession numbers, 3) GenBank gi numbers, 4) Clone Id numbers, 5) the nucleotide sequences of the ESTs 6) the organism, 7) the library name, 8) the name of the lab, and 9) the institution. The output of 'report2est' is a file in FASTA format with all of the information listed above in the first line of each entry except the sequence, which is listed in the second line of each entry. The resulting file is formatted for BLAST using 'pressdb' (available as part of the ncbi tool kit).

To build a gene or part of a gene from ESTs, the program 'makegene' was developed. Input to this program is a query sequence and the organism/species for which a gene is to be built. An initial search of the formatted EST database described above is performed using BLAST (blastn). Any results that contain warnings, such as polyA tails or other repeat elements, are eliminated from future queries. The program 'blast_parse_reports' was developed to extract

the FASTA header line from the search results and the output is then filtered to extract only FASTA header lines for the desired species.

The initial results, having been filtered for warnings and species, go into a loop in which searches against the database are repeated until no new ESTs are found. The loop consists of the following steps: 1) when possible the names of both ends of the ESTs are extracted from the database by searching using the 'Clone Id' field or the part of the '<u>EST name</u>' field before the .r or .s postscript, 2) any ESTs that have been used as queries in previous loops are removed from the current query by the program 'subtract', 3) the resulting list of ESTs is used to extract the sequences from the database by the program batch_parse_fasta, 4) BLAST is run against the database using each sequence, 5) the output files from BLAST containing warnings are removed, 6) the results are filtered by species, and 7) the loop is reentered if there were new ESTs found in the previous pass through the loop.

The ESTs chosen by 'makegene' are used as input for the program 'mpd2_cluster' (Hide, W., Burke, J, and Davison, D. U. of Houston, unpublished) which clusters overlapping sequences. The programs 'contig' (Kerlavage, T., TIGR, unpublished), 'gde2mult' and 'gde2sing' (Smith, S.W., *et al.*, CABIOS 10, 671-675 (1994)), are used to make an alignment and consensus sequence of the overlapping ESTs.

<u>RESULTS</u>

<u>cDNA cloning and characterization of STLK2</u>

The human STLK2 cDNA sequence is composed of two overlapping EST fragments, AA191319 and W16504, that were identified using a Smith-Waterman search of the EST database with STLK1 (MST3 GB:AF024636) as a query. The complete

sequence of both clones was determined and used to generate the full-length human STL2 sequence.

EST clone AA191319 contains a 1327 bp insert and an ORF of 1146 bp (382 amino acids). EST clone W16504 contains a 2474 bp insert (not including the poly-A tail) and an ORF of 687 bp (382 amino acids).

The full-length human STLK2 cDNA (SEQ ID NO. 1) is 3268 bp long. AA191319 spans positions 1-1327 and W16504 positions 743-3216. The overlap between these two clones exhibits 100% sequence identity. The human STLK2 cDNA constains a 1248 bp ORF flanked by a 181 bp 5′ UTR (1-181) and a 1784 bp 3′ UTR (1433-3216) that is followed by a 52 nucleotide polyadenylated region. A polyadenylation signal (AATAAA) is found at positions 3193-3198. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for STLK2. Furthermore, human STLK2, and the related SOK-1 and MST3 proteins, conserve the amino acid sequence immediately following this presumed initiating methionine.

Several EST fragments span the complete STLK2 sequence with AA191319 at the 5′ end and W16504 at the 3′ end.

All searches against the public nucleic acid database (NRN) and protein database (NRP) were conducted using the Smith-Waterman gap alignment program ((Smith, TF and Waterman, MS (1981) J. Mol. Biol, 147, 195-197).) with the PAM100 matrix and gap open and extension penalties of 14:1, respectively.

cDNA Cloning and Characterization of STLK3

A mammalian STLK3 clone, 135-31-19, was first identified from a PCR screen with the degenerate oligos, TRK1 and TRK4, applied to a sscDNA generated from adult rat

brain substantia nigra. Sequence analysis of the 457 bp insert indicated that it represented a novel member of the STE20-subfamily of STKs.

A Smith-Waterman search of the EST database with the rat STLK3 fragment and human STLK1 (MST3 GB:AF024636) as queries identified several overlapping ESTs spanning most of the human STLK3 cDNA sequence. A Makegene analysis generated a 3037 bp contig from approximately 44 EST sequences. Since the 3′ ESTs were not commercially available, a pair of primers (5'-CACAGAAACGGTCAGATTCAC-3′ and 5'-GATCAGGGTGACATCAAGGGAC-3') were derived from this region to generate PCR clone 3R21-20-6 from human fetal liver sscDNA. This clone and EST AA278967 were fully sequenced to generate the full-length STLK2 cDNA sequence.

AA278967 is a 837 bp EST isolated by the IMAGE consortium from cDNA made from CD20+/IgD- germinal center B cells sorted from human tonsillar cells.

PCR clone 3R21-20-6 was isolated from human fetal sscDNA and contains a 1116 bp insert, including a 1086 bp ORF encoding the 362 C-terminal amino acids of STLK3.

The full-length human STLK3 cDNA (SEQ ID NO. 2) is 3030 bp long. AA278967 spans positions 1-814 and 3R21-20-6 spans positions 464-1579. The overlap between these two clones exhibits 100% sequence identity. The remaining 1452 bp of 3′ UTR is derived from an assembly of multiple unconfirmed EST fragments.

The near full-length human STLK3 cDNA (SEQ ID NO.2) is 3030 bp long and consists of a 1548 bp ORF flanked by a 1476 bp 3′ UTR (1550-3025) and a 5 nucleotide polyadenylated region. A polyadenylation signal (AATAAA) begins at position 3004. Since the coding region is open throughout the 5′ extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. Six

copies of a "GGCCCC" repeat were observed in positions 21-67. Five independent ESTs (AA150838, AA286879, AA251679, AA252004, AA278967) showed the same repeat, suggesting that this sequence may be an integral region of the human STLK3 gene. Stronger evidence for this being the case is provided by the sequence of the murine orthologue of STLK3 represented by a 876 bp EST W20737.

Multiple EST fragments span the complete STLK3 sequence with AA278967 at the 5' end and AA628477 and others at the 3' end.

<u>cDNA Cloning and Characterization of STLK4</u>

The human STLK4 cDNA sequence is composed of two overlapping EST fragments, AA297759 and AA100484, that were identified using a Smith-Waterman search of the EST database with STLK1 (MST3 GB:AF024636) as a query. The complete sequence of both clones was determined and used to generate the near full-length human STLK4 sequence.

AA100484 is an IMAGE consortium cDNA clone isolated from the T-84 colonic epithelium cell line. It has an insert of 3694 bp and a coding region of 1146 bp (382 amino acids). A Smith-Waterman sequence alignment against the NRN database showed this EST to be 71.4% identical to the human STE20-like kinase (GB:X99325).

W16504 is an IMAGE consortium clone isolated from a human fetal heart cDNA library. It has an insert length of 2474 bp (not including the poly-A tail) and a coding region of 687 bp (229 amino acids). A Smith-Waterman sequence alignment of W16504 against the NRN database showed this EST to be 69.2% identical to the human STE20-like kinase (GB:X99325).

The full-length human STLK2 cDNA (SEQ ID NO. 1) is 3268 bp long. AA191319 spans positions 1-1327, and W16504

positions 743-3216. The overlap between these two clones is 585 bp long with 100% sequence identity.

AA100484 is an IMAGE consortium cDNA clone isolated from the T-84 colonic epithelium cell line. AA100484 covers the bulk of Human STLK4 with its 3694 bp, which spans positions 146-3839 of SEQ ID NO:3. A second EST, AA297759, isolated from a Jurkat T cell cDNA library, spans positions 1-271 of the human STLK4 contig. The two ESTs overlap over a 126 bp stretch that has only one nucleotide discrepancy at position 149 (G in AA297759 and T in AA100484). A T at this position was chosen for the SEQ ID NO:3 based on sequence data generated from A100484. The 5′ 145 bp of human STLK4 contains three sequencing ambiguities (N′s in SEQ ID NO:3) arising from sequence errors in the GenBank entry for AA297759. Three amino acid sequence ambiguities in the N-terminus of human STLK4 are present also in SEQ ID NO:7 as a consequence of the sequence inaccuracies from the EST entry.

The coding region of human STLK4 is 1242 bp long (2-1243), capable of encoding a 414 amino acid polypeptide, and is followed by a 2596 nucleotide 3′ UTR (1244-3839). Human STLK4 ends in a polyadenylated stretch that has 18 adenines (3840-3857). A polyadenylation signal (AATAAA) is found between positions 3822-3827. Targeted-PCR cloning identified one rat orthologue of human STLK4, clone 135-31-19. In addition, one murine orthologue of human STLK4 was recognized in the EST database as AA117483. None of these orthologues add additional N-terminal sequence to the human STLK4.

The near full-length human STLK4 cDNA (SEQ ID NO.3) is 3857 bp long and consists of a 1242 bp ORF flanked by a 2596 bp 3′ UTR (1244-3839) and an 18 nucleotide polyadenylated region. Polyadenylation signals (AATAAA) begin at positions

2181 and 3822. Since the coding region is open throughout the 5′ extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. A near full-length murine STLK4 cDNA is represented in the 1773 bp EST AA117438. It extends an additional 21 nucleotides 5′ of the human STLK4 consensus, but since its coding region is open throughout the 5′ extent of the sequence, this is also probably a partial cDNA clone lacking the N-terminal start methionine.

Several EST fragments span the complete STLK3 sequence with AA297759 at the 5′ end and AA100484 and others at the 3′ end.

cDNA Cloning and Characterization of STLK5

The human STLK5 cDNA sequence is composed of four overlapping sequences, AI418298, 2R96-13-1, 3R25-45-3 and R46685. A human STLK5 clone, F07734, was first identified using a Smith-Waterman search of the EST database with SPS_sc (U33057) as a query.

AI418298 is an IMAGE consortium cDNA clone with an 895 bp insert.

PCR clone 2R96-13-1 was isolated from human brain sscDNA using primers 5′-CTCATCTGTACACACTTCATGG and 5′-GATTCCCACACTGTAGATGTC derived from F07734. 2R96-13-1 contains a 330 bp insert and an ORF of 330 bp (110 amino acids).

EST clone R46685 was identified using a Smith-Waterman search of the EST database with the C-terminus of SPS_sc (GB:U33057) as query. Sequence analysis of the 1047 bp insert identified this EST to contain an ORF of 285 bp (95 amino acids) encoding the C-terminus of human STLK5.

PCR clone 3R25-45-3 was isolated from human fetal brain sscDNA using primers 5′- GGCCCTCGACTACATCCACCACAT and 5′-

CAACGAAACTAACACAGCATAAGG derived from 2R96-13-1 and R46685, respectively. 3R25-45-3 contains a 330 bp insert and an ORF of 750 bp (250 amino acids).

The full-length human STLK5 cDNA (SEQ ID NO:96) is 2110 bp long and consists of a 1119 bp ORF flanked by a 229 bp 5′ UTR and a 762 bp 3′ UTR. The sequence flanking the first ATG conforms to the Kozak consensus (*supra*) for an initiating methionine, and is believed to be the translational start site for STLK5.

Several EST fragments span the complete STLK5 sequence with AA297059 and F07734 at the 5′ end and R46686 and F03423 and others at the 3′ end.

STLK5 displays a 100% match over a 41 bp stretch (position 2-42, SEQ ID NO. 97) to a human CpG island repeat (Z61277).

cDNA Cloning and Characterization of STLK6

Human STLK6 was first identified in the translated EST database (AA219667) as a novel serine threonine kinase.

The partial human STLK6 cDNA (SEQ ID NO:98) is 2,001 bp long and consists of a 1,254 bp ORF flanked by a 75 bp 5' UTR and a 673 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (Kozak, M., Nucleic Acids Res. 15, 8125-8148 (1987)) for an initiating methionine, and is believed to be the translational start site for STLK6.

At the time of filing, inventors believe that STLK6 does not have any significant match in the nucleic acid database.

cDNA Cloning and Characterization of STLK7

Human STLK7 was first identified in the translated EST database (AA988954) as a novel serine threonine kinase. The

original clone was not available through public sources, so a PCR fragment amplified from the sequence of AA988954 yielded 5R54-21-2.

The partial human STLK7 cDNA (SEQ ID NO:100) is 311 bp long and consists of a 309 bp ORF. Since the coding region is open throughout the 5′ and 3′ extent of this sequence, this appears to be a partial cDNA clone lacking the N-terminal start methionine and C-terminal stop codon.

STLK7 shares 80% sequence identity to human SPAK (AF099989) over a 167 bp region and 50% nucleotide sequence identity to SLTK7 (SEQ ID NO. 101) over 391 nucleotides.

cDNA Cloning and Characterization of ZC1

The human ZC1 cDNA sequence is composed of two overlapping PCR clones, 3R25-24-2 and R65-12-2.

A human ZC1 clone, 125-33-5, was first identified from a PCR screen with degenerate oligos, TRK1 and TRK4, applied to sscDNA generated from human small airway epithelial cells (Clontech). Sequence analysis of the 503 bp insert identified a 501 bp ORF (167 amino acids) with the potential to encode a novel human STK related to the *C. elegans* ZC504.4 gene product.

PCR clone 3R25-24-2 was isolated from human SNB19 glioblastoma sscDNA using primers 5′-ATGGCGAACGACTCTCCCGCGAA and 5′-ACACCAAAATCAACAAGTTTCACCTC derived from the N-terminus of a murine orthologue of ZC1 (NIK, GB:U88984) and the original human ZC1 clone 125-33-5, respectively. 3R25-24-2 contains a 527 bp insert and an ORF of 519 bp (173 amino acids).

PCR clone R65-12-2 was isolated as follows: A Smith-Waterman search of the EST database with the *C. elegans* ZC504.4 gene (GB:Z50029) as a query identified a human EST (W81656) whose ORF is related to the *C. elegans* gene and

terminates in an identical residue (Trp). A primer was designed 3' to this stop codon (5'-AGTTACAAGGAATTCCAAGTTCT) and used in a PCR reaction with a primer derived from the original human ZC1 clone 125-33-5 (5'-ATGAAGAGGAAGAAATCAAACTG) using sscDNA from human SNB19 glioblastoma as a template. PCR clone R65-12-2 was identified and was found to contain a 3611 bp insert with a 3534 bp ORF encoding the C-terminal portion of human ZC1 (1178 amino acids).

The full-length human ZC1 cDNA (SEQ ID NO. 9) is 3798 bp long. Clone 3R25-24-2 spans positions 1-527, and clone R65-12-2 spans positions 188-3798. The overlap between these two clones exhibits 100% sequence identity. The human ZC1 contains a 3717 bp ORF (17-3723) flanked by a 6 bp 5' UTR and a 75 bp (3724-3798) 3' UTR. No polyadenylation signal (AATAAA) or polyadenylated region are present in the 3'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human ZC1.

Multiple EST fragments (W81656) match the 3' end of the human ZC1 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

<u>cDNA Cloning and Characterization of ZC2</u>

The human ZC2 cDNA sequence is composed of four overlapping PCR clones, G75-31-17, R65-24-6, 2R28-8-1, and R99-6-10.

A human ZC2 clone, G75-31-17, was first identified from a PCR screen with degenerate oligos, ROS1 (5'-GCNTTYGGNGARGTNTAYGARGG) and CCK4b (5'-GCTGGATCCYTCNGGNSWCATCCA), applied to sscDNA generated from the human HLT383 primary non-small cell lung cancer tissue.

Sequence analysis of the 492 bp insert identified a 492 ORF (164 amino acids) with the potential to encode a novel human STK related to the *C. elegans* ZC504.4 gene product.

PCR clone R99-6-10 was isolated as follows: A Smith-Waterman search of the EST database with *C. elegans* ZC504.4 gene (GB:Z50029) as a query identified two overlapping human EST fragments (AA115844 and R51245) whose ORFs were related to the *C. elegans* gene and terminate in an identical residue (Trp). A primer was designed 3' to the stop codon found in R51245 (5'-AGATGGACTGTACTGGGAGG) and used in a PCR reaction with a primer derived from AA115844 (5'-ACTTTGTGCAGCTCTGTGGG) using human fetal brain sscDNA as a template. PCR clone R99-6-10 was identified and was found to contain a 1095 bp insert with a 930 bp ORF encoding the C-terminal portion of human ZC2 (310 amino acids).

PCR clone R65-24-6 was isolated from human HT29 colon cancer cell line sscDNA using primers 5'-AAGGTTATGGATGTCACAGGG and 5'-AGATGGACTGTACTGGGAGG derived from G75-31-17 and R51245, respectively. The 3' primer used in this PCR reaction misprimed between positions 1634-1653 of this gene leading to the formation of a truncated product. R65-24-6 contains a 1593 bp insert and an ORF of 1593 bp (531 amino acids).

PCR clone 2R28-8-1 was isolated from human colon cancer cell line HT29 sscDNA using primers 5'-CTCACAAGGTTGCCAACAGG and 5'-AGTCCCCACCAGAAGGTTTAC derived from R65-24-6 and R99-6-10, respectively. 2R28-8-1 contains a 1538 bp insert and an ORF of 1536 bp (512 amino acids).

The partial human ZC2 cDNA (SEQ ID NO. 10) is 4055 bp long. Clone G75-31-17 spans positions 1-492, clone R65-24-6 spans positions 58-1650, clone 2R28-8-1 spans positions 1466-3003 and clone R99-6-10 spans positions 2961-4055. The overlaping regions between these clones exhibit 100%

sequence identity except for a single guanine (G75-31-17) to adenosine (R65-24-6) mismatch at position 280 resulting in a Glu to Lys change. Based on the presence of an acidic residue in this position in human ZC1 and ZC3 and *C. elegans* ZC504.4, the sequence encoding the Glu is probably correct. The human ZC2 gene contains a 3891 bp ORF (1-3891) flanked by 164 bp (3892-4055) 3′ UTR. No polyadenylation signal (AATAAA) or polyadenylated region is present in the 3′UTR.

Multiple EST fragments (R51245) match the 3′ end of the human ZC2 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5′ end.

<u>cDNA Cloning and Characterization of ZC3</u>

The human ZC3 cDNA sequence is composed of four overlapping PCR clones, G75-30-30, 3R33-5-3, 3R19-17-6, and R99-43-11.

A human ZC3 clone, G75-30-30, was first identified from a PCR screen with degenerate oligos, ROS1 and CCK4b, applied to sscDNA generated from a human HLT370 primary non-small cell lung cancer tissue. Sequence analysis of the 492 bp insert identified a 492 ORF (164 amino acids) with the potential to encode a novel human STK related to the *C. elegans* ZC504.4 gene product.

PCR clone R99-43-11 was isolated as follows: A Smith-Waterman search of the EST database with the *C. elegans* ZC504.4 gene (GB:Z50029) as a query identified a human EST (R54563) whose ORF is related to the *C. elegans* gene and terminates in an identical residue (Trp). A primer was designed 3′ to the stop codon found in R54563 (5′-TCAGGGGTCAGAGGTCACG) and used in a PCR reaction with a primer derived from the 5′ end of R54563 (5′-CCCAAACCCTACCACAAATTC) using sscDNA from human fetal brain

as a template. PCR clone R99-43-11 was identified and was found to contain a 719 bp insert with a 564 bp ORF encoding the C-terminal portion of human ZC3 (188 amino acids).

PCR clone 3R19-17-6 was isolated from human A549 lung cancer cell line sscDNA using primers 5'-CCCCCGGGAAACGATGACCA and 5'-AGCCGCTGCCCCTCCTCTACTGT derived from G75-30-30 and R99-43-11, respectively. The 3' primer used in this PCR reaction misprimed leading to the formation of a truncated product. 3R19-17-6 contains a 1172 bp insert and an ORF of 1170 bp (390 amino acids).

PCR clone 3R33-5-3 was isolated from human A549 lung cancer cell line sscDNA using primers 5'-ACCGCAACATCGCCACCTACTAC and 5'-CTCGACGTCGTGGACCACC derived from G75-30-30 and 3R19-17-6, respectively. 3R33-5-3 contains a 2465 bp insert and an ORF of 2463 bp (821 amino acids).

The full-length human ZC3 cDNA (SEQ ID NO. 11) is 4133 bp long. Clone G75-30-30 spans positions 1-483, clone 3R33-5-3 spans positions 134-2598, clone 3R19-17-6 spans positions 2356-3512 and clone R99-43-11 spans positions 3415-4133. The overlaps between these clones exhibit 100% sequence identity. The human ZC3 gene contains a 3978 bp ORF (1-3978) flanked by a 152 bp 3' UTR (3979-4133). No polyadenylation signal (AATAAA) or polyadenylated region is present in the 3'UTR.

Multiple EST fragments (R54563) match the 3'end of the human ZC3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

cDNA Cloning and Characterization of ZC4

The human ZC4 cDNA sequence, represented by PCR fragment 3R25-27-1, was first identified in the human genomic cosmid 82J11 (GB:Z833850) containing exon sequences that displayed strong homology to the ZC504.4 *C. elegans* gene.

PCR clone 3R25-27-1 was isolated from human fetal liver sscDNA and primers 5'-CAATGTTAACCCACTCTATGTCTC and 5'-AGTTTGCCGATGTTTTTCTTTTC derived from a potential ORF (positions 25729-25852) from the 82J11 cosmid and from an EST (R98571) encoding the C-terminus of the human ZC4 gene, respectively.

The partial human ZC4 cDNA (SEQ ID NO.12) is 1459 bp long and consists of a 1047 bp ORF (2-1048) flanked by a 411 bp (1049-1459) 3'UTR region. No polyadenylation signal (AATAAA) or polyadenylated region is present in the 3'UTR.

The N-terminal coding sequence for ZC4_h was extended by building a contiguous DNA sequence of 233,137 bp containing Z83850 and four other sequences: cU84B10 and cU230B10 (from the Sanger Human Genome Sequencing Project, http://www.sanger.ac.uk/HGP/) and Z97356 and Z69734 (available from the National Institute for Biotechnology Information, http://www.ncbi.nlm.nih.gov/Entrez/nucleotide.html). The position of each sequence in the contig is represented in the table below.

Accession	Length	Start	End
cU84B10	43273	0	43273
Z97356	21848	43171	65018
Z69734	37077	63073	100149
cU230B10	11841	88416	100256
Z83850	132981	100156	233137

Sequences in ZC4 genomic contig.

The 233,137 bp contig was analyzed for exons using the programs FGENES 1.5 and FGENESH, human gene structure prediction software available from The Sanger Centre (http://genomic.sanger.ac.uk/gf/gf.shtml).

The resulting human ZC4 coding sequence (SEQ ID NO:104) is 3,681 bp long (excluding the stop codon) and encodes for a STE20 kinase of 1227 amino acids.

cDNA Cloning and Characterization of KHS2

The human KHS2 cDNA sequence is composed of four overlapping clones, 3R25-51-2, 3R16-34-2, 3R16-31-2, and T79916.

A human KHS2 clone, AA250855, was first identified using a Smith-Waterman search of the EST database with KHS1 (GB:U77129) as a query. Sequence analysis of the 1112 bp insert identified a 618 bp ORF (206 amino acids) with the potential to encode a novel STK related to the human KHS1 gene product. Using AA250855 as a query, a second EST (AA446022) was found whose sequence was shown to contain the initiator methionine for human KHS2 based on a comparison with KHS1.

PCR clone 3R25-51-2 was isolated from human testicular cancer sscDNA using primers 5'-CCGCCATGAACCCCGGCTT and 5'-CGATTGCCAAAGACCGTGTCA derived from AA446022 and AA250855, respectively. 3R25-51-2 contains an 850 bp insert and an ORF of 849 bp (283 amino acids).

EST clone, T79916, was identified using a Smith-Waterman search of the EST database with the C-terminus of KHS1 (GB:U77129) as a query. Sequence analysis of the 2107 bp insert identified this EST to contain an ORF of 345 bp (115 amino acids disrupted by a single stop codon) encoding the C-terminus of human KHS2, followed by 1762 bp 3'UTR.

PCR clone 3R16-34-2 was isolated from human testis sscDNA using primers 5'-AGAAGTTGCAGCTGTTGAGAGGA and 5'-TATGGCCCGTGTAAGGATTTC derived from AA250885 and T79916, respectively. 3R16-34-2 contains an 1516 bp insert and an ORF of 1128 bp (376 amino acids).

PCR clone 3R16-31-2 was isolated from normal human colon sscDNA using primers 5'- GTGCCAGAAGTGTTGTGTTGTAA and 5'-TATGGCCCGTGTAAGGATTTC derived from EST T79916. 3R16-31-2 contains a 728 bp insert and an ORF of 669 bp (223 amino acids). This clone lacked the stop codon present within EST T79916 (postion 2662 in the KHS2 sequence).

The full-length human KHS2 cDNA (SEQ ID NO.17) is 4023 bp long. Clone 3R25-51-2 spans positions 1-855, clone AA250885 spans positions 336-923, clone 3R16-34-2 spans positions 545-2061, and clone T79916 spans positions 1917-4023. The overlaping regions between these clones exhibit 100% sequence identity, except for 4 nucleotide differences, two of which are silent, a third corrects the internal stop codon at position 2662, and the fourth at position 247 (T to C change) results in a Pro to Leu change. The human KHS2 cDNA contains a 2682 bp ORF (6-2687) flanked by a 5 bp (1-5) 5'UTR and a 1336 bp (2688-4023) 3' UTR. A potential polyadenylation signal (AATAAA) is found at positions 4008-4013. No polyadenylated region is present in the 3'UTR. The sequence flanking the first ATG is in a poor context for translational initiation, however, a 134 bp 5'UTR sequence from EST AA446022 did not reveal any additional ATG's and displayed two in-frame stop codons 5' to the putative start ATG for human KHS2.

Multiple EST fragments match the 5'end (AA446022) as well as the 3' end (R37625) of the human KHS2 gene.

cDNA Cloning and Characterization of SULU1

The human SULU1 cDNA sequence is composed of three overlapping clones, N40091, 2R90-1-1 and R90907.

A human SULU1 clone, N40091, was first identified using a Smith-Waterman search of the EST database with the *C. elegans* SULU gene (GB: U32275) as a query. Sequence analysis of the 1321 bp insert identified a 906 bp ORF (302 amino acids) with the potential to encode a novel human STK related to the *C. elegans* SULU gene product.

EST clone R90907 was first identified using a Smith-Waterman search of the EST database with the 3' end of the *C. elegans* SULU gene (GB: U32275) as a query. Sequence analysis of the 1647 bp insert identified a 578 bp ORF (192 amino acids) with the potential to encode the C-terminus of the human SULU1 gene product.

PCR clone 2R90-1-1 was isolated from human HT29 colon cancer cell sscDNA using primers 5'- TATTGAATTGGCGGAACGGAAG and 5'- TTGTTTTGTGCTCATTCTTTGGAG derived from N40091 and R90907, respectively. 2R90-1-1 contains a 1625 bp insert and an ORF of 1623 bp (541 amino acids).

The full-length human SULU1 cDNA (SEQ ID NO.19) is 4177 bp long Clone N40091 spans positions 1-1321, clone 2R90-1-1 spans positions 1048-2671, and clone R90907 spans positions 2531-4177. The overlaping regions between these clones exhibit 100% sequence identity. The human SULU1 cDNA contains a 2694 bp ORF (415-3108) flanked by a 414 bp (1-414) 5'UTR and a 1069 bp (3109-4177) 3' UTR followed by a 19 nucleotide polydenylated region. A potential polyadenylation signal (AATAAA) is found at positions 4164-4169. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human SULU1.

Multiple EST fragments match the 5'end (N27153) as well as the 3' end (R90908) of the human SULU1 gene.

cDNA Cloning and Characterization of Murine SULU3

The murine SULU3 cDNA sequence is represented by PCR fragment 2R92-1-6.

A murine SULU3 clone, G83-4-5, was first identified from a PCR screen with degenerate oligos, CCK4c and CCK4b, applied to sscDNA generated from murine day-12 embryos. Sequence analysis of the 473 bp insert identified a 471 ORF (157 amino acids) with the potential to encode a novel human STK related to the *C. elegans* SULU gene (GB: U32275) product. The antisense strand of G83-4-5 is identical at the nucleic acid level to the 5'UTR of the murine ets1 protooncogenic transcription factor (GB:X53953). This homology is likely the result of a cloning artifact attached to the 5'-end of the database entry for murine ets1.

PCR clone 3R19-17-6 was isolated from human A549 cell sscDNA using primers 5'-CCCCCGGGAAACGATGACCA and 5'-AGCCGCTGCCCCTCCTCTACTGT derived from G75-30-30 and R99-43-11, respectively. The 3' primer used in this PCR reaction misprimed leading to the formation of a truncated product. 3R19-17-6 contains a 1172 bp insert and an ORF of 1170 bp (390 amino acids).

PCR clone 2R92-1-6 was isolated from murine d8 embryo sscDNA using primers 5'-ACCGCAACATCGCCACCTACTAC and 5'-GATTGCTTTGTGCTCATTCTTTGG derived from the 5' UTR of the ets1 gene and the human EST AA234623, respectively. The latter (shown herein) encodes the C-terminus of human SULU3. 2R92-1-6 contains a 2249 bp insert and an ORF of 2244 bp (748 amino acids).

The partial murine SULU3 cDNA (SEQ ID NO.21) is 2249 bp long and consists of a 2244 bp ORF (6-2249) flanked by a 5

bp (1-5) 5'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for murine SULU3.

One EST fragment (AA446022) matches the 3' end of the partial murine SULU3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

cDNA Cloning and Characterization of Human SULU3

The human SULU3 cDNA sequence is composed of two overlapping clones, 2R90-22-1 and AA234623.

A human SULU3 clone, AA234623, was first identified using a Smith-Waterman search of the EST database with the *C. elegans* SULU gene (GB: U32275) as a query. Sequence analysis of the 2652 bp insert identified a 1185 bp ORF (395 amino acids) with the potential to encode the C-terminus of a novel human STK related to the *C. elegans* SULU gene product.

PCR clone 2R90-22-1 was isolated from human SKMel128 melanoma cell line sscDNA using primers 5'-TATTGAATTGGCGGAACGGAAG and 5'- TTGTTCTAAGAGTGCCCTCCG derived from the murine SULU3 2R92-1-6 clone and from AA234623, respectively. 2R92-1-6 contains a 1897 bp insert and an ORF of 1896 bp (632 amino acids).

The partial human SULU3 cDNA (SEQ ID NO.20) is 3824 bp long. Clone 2R90-22-1 spans positions 1-1897 and clone AA234623 spans positions 1173. The overlaping region between these clones exhibits 100% sequence identity. The human SULU3 cDNA contains a 2358 bp ORF (2-2359) flanked by a 1465 bp (2360-3824) 3'UTR followed by a 19 nucleotide polydenylated region. A potential polyadenylation signal (AATAAA) is found at positions 2602-2607. Since the coding

region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine.

Multiple EST fragments (R02283) match the 3'end of the human SULU3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

cDNA Cloning and Characterization of GEK2

The human GEK2 cDNA sequence is composed of three overlapping clones, AA459448, 3R25-48-1 and GEK2_h#3.

A human GEK2 clone, AA459448, was first identified using a Smith-Waterman search of the EST database with the human SLK gene (GB: AB002804) as a query. Sequence analysis of the 1286 bp insert identified a 1227 bp ORF (409 amino acids) with the potential to encode the N-terminus of a novel human STK related to the human SLK gene product. An additional Smith-Waterman search using the C-terminus of the SLK gene as a query yielded three additional EST's, AA323687, AA380492 and AA168869, that encode the C-terminal region of human GEK2.

PCR clone 2R98-41-17 was isolated from human testis sscDNA using primers 5'- AAGACCATGCCGTGCGCCG and 5'-ATTCCTTCAGGTTCTGGTTATGG derived from AA323687 and from AA380492, respectively. 2R98-41-17 contains a 851 bp insert and an ORF of 849 bp (283 amino acids).

PCR clone GEK2_h#3 was isolated from human sscDNA made from the H23 tumor cell line using primers 5'-GCAGCAAGTGGAGAAGATGG and 5'- GGAAGCATCCCCAGAGCTGTAG derived from the sequence of clone 3R25-48-1 and from the 3' end of murine LOK (GB:D89728), respectively. GEK2_h#3 contains a 1042bp insert and an ORF of 1041 bp (347 amino acids).

The full-length human GEK2 cDNA (SEQ ID NO:106) is 2962 bp long. Clone AA459448 spans positions 1-1286, clone 3R25-48-1 spans positions 1100-2449 and clone GEK2_h#3 spans positions 1920-2962. The overlapping regions between these clones exhibit 100% sequence identity.

The human GEK2 cDNA contains a 2904 bp ORF (59-2962) flanked by a 58 bp (1-58) 5'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human GEK2.

Multiple EST fragments (AA465671) match the 5'end of the sequence, but only one (AA380492) matches the 3' end of the human GEK2 gene.

cDNA Cloning and Characterization of PAK4

The human PAK4 cDNA sequence is represented by clone SNB2#1.

A human PAK4 clone, R88460, was first identified using a Smith-Waterman search of the EST database with the human PAK gene (GB: U24152) as a query. Sequence analysis of the 2332 bp insert identified a 930 bp ORF (310 amino acids) with the potential to encode the C-terminus of a novel human STK related to the human PAK gene product.

cDNA clone SNB2#1 was isolated from human glioblastoma cell line SNB75 cDNA library using a probe derived from R88460. SNB2#1 contains a 3604 bp insert and an ORF of 2043 bp (681 amino acids).

The full-length human PAK4 cDNA (SEQ ID NO.27) is 3604 bp long and consists of a 2043 bp ORF (143-2185) flanked by a 142 bp (1-142) 5'UTR and a 1419 3' UTR followed by a 22 nucleotide polydenylated region. A potential polyadenylation signal (AATTAAA) is found at positions 3582-3588. The sequence flanking the first ATG conforms to the

Kozak consensus for an initiating methionine, and is believed to be the translational start site for human PAK4. The 3' UTR of the PAK4 gene contains a GT dinucleotide repeat prone to undergo expansion based on the number of repeats found in clones SNB#1 and R88460, 32 and 23, respectively. Several neurologic disorders have been correlated with the expansion of di- or tri-nucleotide repeats similar to those found in the PAK4 sequence, suggesting PAK 4 may also be a disease target and that this repeat in its 3'UTR may serve as a diagnostic marker.

Multiple EST fragments (AA535791) match the 3'end of the human PAK4 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

cDNA Cloning and Characterization of PAK5

The full-length human PAK5 cDNA sequence is composed of two overlapping clones, H450#1-1 and SNB8#5.

A human PAK5 clone, R18825, was first identified using a Smith-Waterman search of the EST database with the human PAK4 gene as a query. Sequence analysis of the 1248 bp insert identified a 420 bp ORF (140 amino acids) with the potential to encode the C-terminus of a novel human STK related to the human PAK4 gene product.

cDNA clone SNB8#5 was isolated from human SNB75 cDNA library using a probe derived from R18825. SNB2#1 contains a 2028 bp insert and an ORF of 1194 bp (398 amino acids).

The partial human PAK5 cDNA (SEQ ID NO.28) is 2028 bp long and consists of a 1194 bp ORF (2-1195) flanked by an 833 bp (1196-2028) 3'UTR followed by a 22 nucleotide polydenylated region. A potential polyadenylation signal (AATTAAA) is found at positions 2004-2010. Since the coding region is open throughout the 5' extent of this sequence,

this is apparently a partial cDNA clone lacking the N-terminal start methionine.

Clone H460#1-1 was isolated from a human lung H460 cDNA library using a probe derived from the partial SNB2#1 cDNA clone described above. Sequence analysis of the 2526 bp insert identified a 1773 bp ORF (592 amino acids) with the potential to encode a full-length PAK5.

The human PAK5 cDNA (SEQ ID NO:102) is 2,806 bp long and consists of a 1,773 bp ORF flanked by a 201 bp 5' UTR and a 833 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (Kozak, M., Nucleic Acids Res. 15, 8125-8148 (1987)) for an initiating methionine, and is believed to be the translational start site for PAK5.

PAK5 shares 99% sequence identity over 2795 bp to a recent database entry, AF005046. These sequences are presumed to be from the same gene, with minor polymorphic variations.

EXAMPLE 2: Expression Analysis of Mammalian STE20-related Protein Kinases

Materials and Methods

Northern blot analysis

Northern blots were prepared by running 10 g total RNA isolated from 60 human tumor cell lines (HOP-92, EKVX, NCI-H23, NCI-H226, NCI-H322M, NCI-H460, NCI-H522, A549, HOP-62, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, IGROV1, SK-OV-3, SNB-19, SNB-75, U251, SF-268, SF-295, SF-539, CCRF-CEM, K-562, MOLT-4, HL-60, RPMI 8226, SR, DU-145, PC-3, HT-29, HCC-2998, HCT-116, SW620, Colo 205, HTC15, KM-12, UO-31, SN12C, A498, CaKi1, RXF-393, ACHN, 786-0, TK-10, LOX IMVI, Malme-3M, SK-MEL-2, SK-MEL-5, SK-MEL-28, UACC-62, UACC-257, M14, MCF-7, MCF-7/ADR RES, Hs578T, MDA-MB-231, MDA-MB-435, MDA-N, BT-549, T47D), from 22 human adult tissues (thymus, lung,

duodenum, colon, testis, brain, cerebellum, cortex, salivary gland, liver, pancreas, kidney, spleen, stomach, uterus, prostate, skeletal muscle, placenta, mammary gland, bladder, lymph node, adipose tissue), and 2 human fetal normal tissues (fetal liver, fetal brain), on a denaturing formaldehyde 1.2% agarose gel and transferring to nylon membranes.

Filters were hybridized with random primed [α^{32}P]dCTP-labeled probes synthesized from the inserts of several of the STE20-related kinase genes. Hybridization was performed at 42 °C overnight in 6X SSC, 0.1% SDS, 1X Denhardt's solution, 100 µg/mL denatured herring sperm DNA with 1-2 x 10^6 cpm/mL of ^{32}P-labeled DNA probes. The filters were washed in 0.1X SSC/0.1% SDS, 65 °C, and exposed on a Molecular Dynamics phosphorimager.

Quantitative PCR analysis

RNA was isolated from a variety of normal human tissues and cell lines. Single stranded cDNA was synthesized from 10 µg of each RNA as described above using the Superscript Preamplification System (GibcoBRL). These single strand templates were then used in a 25 cycle PCR reaction with primers specific to each clone. Reaction products were electrophoresed on 2% agarose gels, stained with ethidium bromide and photographed on a UV light box. The relative intensity of the STK-specific bands were estimated for each sample.

DNA Array Based Expression Analysis

Plasmid DNA array blots were prepared by loading 0.5 µg denatured plasmid for each STE20-related kinase on a nylon membrane. The [α^{32}P]dCTP labeled single stranded DNA probes were synthesized from the total RNA isolated from several

human immune tissue sources or tumor cells (thymus, dendrocytes, mast cells, monocytes, B cells (primary, Jurkat, RPMI8226, SR), T cells (CD8/CD4+, TH1, TH2, CEM, MOLT4), K562 (megakaryocytes). Hybridization was performed at 42 °C for 16 hours in 6X SSC, 0.1% SDS, 1X Denhardt's solution, 100 µg/mL denatured herring sperm DNA with 10^6 cpm/mL of [α^{32}P]dCTP labeled single stranded probe. The filters were washed in 0.1X SSC/0.1% SDS, 65 °C, and exposed for quantitative analysis on a Molecular Dynamics phosphorimager.

RESULTS

Distribution of STE20-Related Gene Transcripts in Normal Tissues and Tumor Cell Lines

ZC1, ZC2, and ZC3 RNA expression was analyzed by quantitative PCR from multiple human normal tissues, cultured primary epithelial and endothelial cells, and tumor cell lines. The results are summarized in Tables 1 and 2, with relative expression values ranging from 0 (undetectable) to 23 (very strong). An "x" refers to sample not tested. ZC1, ZC2, and ZC3 were all expressed at very low levels in most normal human tissues, however ZC1 and ZC2 were more abundant in cultured epithelial cells and ZC3 in normal kidney and breast tissue.

Expression of these 3 genes was also examined in a panel of human tumor cell lines representing a diverse sampling of tumor types (Table 2). ZC1 and ZC2 showed strong expression in cell lines from most melanomas and renal tumors and from some non-small cell lung cancers and colon tumors. ZC3 expression was consistently lower in the tumor cell lines except for high expression in most breast cancers and leukemias. The robust overexpression ZC1, ZC2,

and ZC3 in tumor cells versus normal tissues may provide an attractive target for oncology drug development.

Expression of all the novel STE20-related kinases was examined in a panel of human immune tissues/cells by hybridization to a DNA array blot containing plasmids encoding each of these genes. STLK2 was broadly expressed in all 14 immune samples, whereas STLK4 and PAK4 were highly expressed in a subset of 6-7 of the samples (Table 3). Several other kinases (SULU3, ZC4, KHS2) had more restricted expression, while others were expressed in only a single immune source (STLK3, thymus; ZC1, dendrocytes; ZC3, monocytes; PAK5, mast cells and MOLT4), and several more were absent from all the immune sources assayed (GEK2, SULU1, ZC2, STLK5). These expression patterns were quite distinct among members of the same subfamily (*i.e.*, ZC1, ZC2, ZC3 and ZC4, or PAK1, PAK2, PAK3, PAK4, PAK5). This analysis suggests that some of these kinases may be candidate targets for various immune disorders, and that some, which are more broadly expressed, may mediate functions vital to the basic biology of most proliferating cells.

TABLE 1

ZC1, ZC2 and ZC3 Expression in Normal Human Tissues and Cells

Sample		ZC1	ZC2	ZC3
NORMAL				
Brain	Tiss	2.8	0.6	0.9
Duod	Tiss	3.8	1.5	0.3
Heart	Tiss	1.2	0.3	0.0
Kidney	Tiss	0.7	0.0	7.0
Lung	Tiss	1.6	0.2	0.0
Pancreas	Tiss	2.0	0.4	2.5

Placenta	Tiss	1.4	0.0	0.0
Sal gl.	Tiss	3.0	0.3	3.2
Sk mus.	Tiss	2.3	0.1	0.1
Spleen	Tiss	0.4	0.0	x
Stomach	Tiss	0.8	0.0	0.0
Thymus	Tiss	3.5	0.4	1.5
Cereb	Tiss	2.8	1.1	4.4
Liver	Tiss	1.8	0.0	0.4
Uterus	Tiss	1.6	0.0	1.4
Prostate	Tiss	1.4	0.0	1.6
Testis	Tiss	x	x	5.8
f Brain	Tiss	x	x	3.1
Mam gl	Tiss	x	x	7.2
HCAEC	ENDO	1.0	0.0	0.0
HMVEC-d	ENDO	0.7	0.0	0.4
HMVEC-L	ENDO	2.2	1.6	1.8
HPAEC	ENDO	9.3	5.3	6.4
HMEC	EPI	4.1	2.3	1.9
RPTEC	EPI	3.6	2.2	0.2
HRCE	EPI	5.3	3.5	1.3
HSAE	EPI	0.9	3.3	4.8

TABLE 2

ZC1, ZC2 and ZC3 Expression in Tumor Cell lLnes

Sample	Origin	ZC1	ZC2	ZC3
HOP-92	Lung	9.3	7.2	3.3
EKVX	Lung	10.7	3.7	3.5
NCI-H23	Lung	5.8	6.3	4.1
NCI-H226	Lung	6.5	6.8	3.3

Sample	Origin	ZC1	ZC2	ZC3
HCC-2998	Colon	2.4	3.8	3.0
HCT 116	Colon	2.2	2.1	5.4
SW-620	Colon	7.8	12.1	3.1
COLO 205	Colon	9.1	16.2	3.0

NCI-H322M	Lung	3.5	5.8	4.9
NCI-H460	Lung	4.5	3.7	2.9
NCI-H522	Lung	4.7	3.3	4.6
A549/ATCC	Lung	3.8	3.6	4.1
HOP-62	Lung	4.3	3.8	4.2
OVCAR-3	Ovary	2.9	3.1	1.5
OVCAR-4	Ovary	3.3	1.0	3.8
OVCAR-5	Ovary	2.6	3.6	2.2
OVCAR-8	Ovary	3.6	2.0	4.7
IGROV1	Ovary	3.8	1.7	3.2
SK-OV-3	Ovary	4.9	0.0	3.5
SNB-19	CNS	5.1	5.4	4.2
SNB-75	CNS	2.5	0.9	0.7
U251	CNS	1.5	1.2	0.6
SF-268	CNS	5.8	2.7	3.0
SF-295	CNS	6.4	1.1	3.2
SF-539	CNS	5.1	2.9	4.3
CCRF-CEM	Leuk	3.4	2.7	3.1
K-562	Leuk	4.1	6.3	4.3
MOLT-4	Leuk	7.1	3.4	4.2
HL-60	Leuk	x	x	0.4
RPMI 8226	Leuk	0.5	0.2	1.4
SR	Leuk	3.5	7.2	5.4
DU-145	Pro	x	x	3.4
PC-3	Pro	x	x	3.4
HT-29	Colon	2.4	5.9	6.6

HCT-15	Colon	13.8	4.9	2.5
KM-12	Colon	7.0	13.2	3.1
UO-31	Colon	10.4	10.6	0.9
SN12C	Renal	8.1	3.4	2.8
A498	Renal	6.2	3.1	2.9
Caki-1	Renal	9.2	14.4	2.3
RXF 393	Renal	10.6	4.8	2.8
ACHN	Renal	9.3	6.0	3.9
786-0	Renal	8.8	15.6	5.6
TK-10	Renal	20.9	21.2	5.0
LOX IMVI	Mel	2.3	2.4	3.3
Malme-3M	Mel	x	x	2.2
SK-MEL-2	Mel	15.7	14.1	2.9
SK-MEL-5	Mel	7.9	7.0	0.0
SK-MEL-28	Mel	16.5	23.1	0.0
UACC-62	Mel	12.1	18.3	5.3
UACC-257	Mel	10.8	9.4	6.2
M14	Mel	4.4	0.9	7.9
MCF7	Breast	4.8	1.3	7.7
MCF-7/ADR	Breast	8.8	3.4	7.7
Hs 578T	Breast	6.9	2.6	5.7
MDA-MB-231	Breast	5.7	1.9	6.4
MDA-MB-435	Breast	4.8	6.7	9.1
MDA-N	Breast	7.3	6.3	9.1
BT-549	Breast	3.6	1.9	8.0
T-47D	Breast	0.4	12.3	9.3

Table 3: STE20-related kinase expression in a human immune panel

KINASE	thymus	Dendro-cytes	Mast cells	Mono-cytes	B cells	CD8+ CD4+	TH1	TH2
GEK2	350	350	350	350	350	350	350	350
SULU1	350	350	350	350	350	350	350	350
SULU3	350	350	350	350	12149	350	5115	350
STLK2	117770	13771	27620	92036	18305	39109	5408	3564
STLK3	8624	350	350	350	350	350	350	350
STLK4	8524	350	350	350	350	8685	5642	350
STLK5	xxx	xxx	xxx	xxx	350	350	350	xxx
ZC1	350	3377	350	350	350	350	350	350
ZC2	350	350	350	350	350	350	350	350
ZC3	350	350	350	20156	350	350	350	350
ZC4	xxx	xxx	xxx	xxx	350	350	350	xxx
KHS2	8766	2508	350	56575	350	350	350	350
PAK4	32658	7684	3729	100948	350	350	350	1604
PAK5	350	350	4905	350	350	350	350	350

KINASE	CEM (T cell)	MOLT4 (T cell)	JURKAT (B cell)	RPMI8226 (B cell)	SR (B cell)	K562 (MO)
GEK2	350	350	350	350	350	350
SULU1	350	350	350	350	350	350
SULU3	350	350	350	350	350	350
STLK2	47236	53262	47605	22560	65936	30390
STLK3	350	350	350	350	350	350
STLK4	3648	350	26772	1570	350	350
STLK5	350	350	350	xxx	350	350
ZC1	350	350	350	350	350	350

ZC2	350	350	350	350	350	350
ZC3	350	350	350	350	350	350
ZC4	1094	7813	14945	xxx	350	6385
KHS2	350	350	350	350	350	350
PAK4	350	10246	350	3229	350	350
PAK5	350	12672	350	350	350	350

Transcript size from Northern data

Kinase	(kb)
STLK2	3.8
STLK4	5.0
ZC1	6.9/4.7
ZC2	6.0/8.0
ZC4	5
KHS2	4.4
SULU1	4.5
SULU3	10.0
GEK2	5.5
PAK4	4.8
PAK5	3.5

STLK2is widely expressed; the highest expression levels were found in placenta, spleen and PBL.

STLK4 is also widely expressed in normal tissues including heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, spleen, thymus, prostate, testis, ovary, small intestine, colon, and peripheral blood lymphocytes. STLK4 was also detected in Jurkat T cells.

ZC1 is highly overexpressed in the following human cancer cell lines: HOP-92, EKVX, NCI-H23, NCI-H226, NCI-H322M, NCI-H522, A549, HOP-62 (lung); OVCAR-3, OVCAR-4, OVCAR-5 (ovary); SNB-19, U251, SF-268, SF-295, SF-539 (CNS); K-562, RPMI-8226 (leukemia); DU-145, PC-3 (prostate); HT-29, HCC-2998, HCT-116, SW620, COLO-205, HCT-15, KM-12 (colon); UO-31, CAKi-1, RXF-393, 786-0, TK-10 (renal); LOXIMVI, Malme-3M, SK-MEL-2, SK-MEL-28, UACC-62, UACC-257, M14

(melanoma); and MCF-7, MCF-7/ADR, HIS 578T, MDA-MB-231, MDA-MB-431, MDA-N, BT-549, T-47D (breast).

ZC2 is expressed in brain and testis. It is highly overexpressed in the following human cancer cell lines: TK-10 (renal); SK-MEL-28, UACC-62 (melanoma); T47D (breast).

Moderate expression in HOP92 (lung); OVCAR4, IGROV1 (ovary); DNB75, U251 (brain); K-562 (leukemia); and COLO205 (colon).

SULU1 is overexpressed in the following human cancer cell lines: HOP-92, EKVX, NCI-H23, NCI-H226, NCI-H322M, NCI-H522, A549, HOP-62 (lung); OVCAR-3, OVCAR-4, OVCAR-5, SK-OV-3 (ovary); SNB-19, U251, SF-268, SF-295, SF-539 (CNS); K-562, RPMI-8226 (leukemia); DU-145, PC-3 (prostate); HT-29, HCC-2998, HCT-116, SW620,. COLO-205, HCT-15, KM-12 (colon); UO-31, CAKi-1, RXF-393, 786-0, TK-10 (renal); LOX, IMVI, Malme-3M, SK-MEL-2, SK-MEL-28, UACC-62, UACC-257, M14 (melanoma); MCF-7, MCF-7/ADR, HIS 578T, MDA-MB-231, MDA-MB-431, MDA-N, BT-549, T-47D (breast)

SULU3 showed a broad pattern of expression in the normal tissue panel of RNAs.

GEK2 was expressed in spleen, thymus and testis. Expression was high in the cell lines RBL-2H3 and H441.

PAK4 was expressed in the normal tissues: brain, testis and prostate, and in the human cancer cell lines: HNCI-H23 (lung); OVCAR-3 (ovary); SNB-19, U251 (CNS); RPMI-8226 (leukemia); DU-145 (prostate); COLO-205, HCT-15 (colon).

PAK5 showed weak expression levels in the normal tissues: brain, testes, bladder, colon, adrenal medulla, spleen, fetal liver, breast, cerebral cortex, cerebellum, thymus, salivary gland, lung, stomach, duodenum, uterus, prostate, skeletal muscle and placenta. PAK5 was overexpressed in the human cancer cell lines: HOP-92, EKVX, NCI-H23, NCI-H226, NCI-H322M, NCI-H522, A549, HOP-62 (lung);

OVCAR-3, OVCAR-4, OVCAR-5, SK-OV-3 (ovary); SNB-19, U251, SF-268, SF-295, SF-539 (CNS); K-562, RPMI-8226 (leukemia); DU-145, PC-3 (prostate); HT-29, HCC-2998, HCT-116, SW620, COLO-205, HCT-15, KM-12 (colon); UO-31, CAKi-1, RXF-393, 786-0, TK-10 (renal); LOXIMVI, Malme-3M, SK-MEL-2, SK-MEL-28, UACC-62, UACC-257, M14 (melanoma); MCF-7, MCF-7/ADR, HIS 578T, MDA-MB-231, MDA-MB-431, MDA-N, BT-549, T-47D (breast).

EXAMPLE 3: STE20-related Protein Kinase Gene Expression Vector Construction

Materials and Methods

Expression Vector Construction

Several expression constructs were generated for some of the human STE20-related cDNAs including: a) full-length clones in a pCDNA expression vector; b) a GST-fusion construct containing the catalytic domain of the novel STE20-related kinase fused to the C-terminal end of a GST expression cassette; and c) a full-length clone containing a Lys to Ala (K to A) mutation at the predicted ATP binding site within the kinase domain, inserted in the pCDNA vector.

The "K to A" mutants of the STE20-related kinase might function as dominant negative constructs, and will be used to elucidate the function of these novel STKs.

RESULTS

Constructs for ZC1, ZC2, ZC3, SULU1, SULU3, PAK4 and PAK5 have been generated.

Numerous additional constructs have been generated for the various STE20-subfamily kinases, including full length, kinase inactive and tagged versions. In addition, the following three constructs were designed for specific applications based on their unique domain structure:

Construct 1: SULU1-coiled-coil2
Vector: pGEX-4T
Insert: Coiled-coil2
Sequence: Amino acids 752-898
Purpose: phage display
Result: Interacts with GEK2 CC1

Construct 2: SULU3-coiled-coil2
Vector: pGEX4T
Insert: coiled-coil 2 domain fused to GST
Sequence range of insert: amino acids 802-898 of SEQ
Purpose: phage display
Result: Interacts with coiled-coiled region of human SLK

Construct 3: PAK5 Dominant Negative
Vector: pCAN5
Insert: Full length coding sequence of human PAK5 containing the following mutation: K350,351A (Lys at aa positions 350 and 351 changed to Ala).
Purpose: to determine role of human PAK5 kinase activity in cell growth and transformation.
Result: Interferes with Ras transformation.

EXAMPLE 4: Generation of Specific Immunoreagents to STE20-Related Protein Kinases

Materials and Methods

Specific immunoreagents were raised in rabbits against KLH- or MAP-conjugated synthetic peptides corresponding to the human STE20-related kinases. C-terminal peptides were conjugated to KLH with glutaraldehyde, leaving a free C-terminus. Internal peptides were MAP-conjugated with a blocked N-terminus. Additional immunoreagents can also be generated by immunizing rabbits with the bacterially expressed

GST-fusion proteins containing the cytoplasmic domains of each novel STK.

The various immune sera are first tested for reactivity and selectivity to recombinant protein, prior to testing for endogenous sources.

Western blots

Proteins in SDS PAGE are transferred to immobilon membrane. The washing buffer is PBST (standard phosphate-buffered saline pH 7.4 + 0.1% triton x 100). Blocking and antibody incubation buffer is PBST +5% milk. Antibody dilutions varied from 1:1000 to 1:2000.

RESULTS

Three SULU1 antisera (against both 539A and 540A) and two SULU3 antisera (542A) reacted specifically with the peptide antigens. Antisera binding was competable with peptide. Experiments with extracts from cells transfected with epitope-tagged SULU1 and SULU3 genes are underway.

Antisera against the PAK4 C-terminal peptide 554A reacted with purified Gst-PAK4 and detected a protein of the correct molecular weight from tissue culture cells. Specific immunoprecipitation experiments are ongoing to determine the reactivity with native protein.

Similar immunization and antisera testing experiments are underway for each of the other novel STE20-kinases.

STE20-related protein kinase peptide immunogens and their specificity in recognizing endogenous protein by Western blots or immunoprecipitations.

Protein	Sequence	Aa positions	Conj	West.	IP
STLK2	EKFQKCSADESP	405-416	KLH	Y	Y
STLK4	SISNSELFPTTDPVGT	252-267	KLH	Y	Y
SULU1	LDFPKEDYR	890-898	KLH	Y	Y
SULU1	HGDPRPEPRPTQ	409-420	KLH	Y	Y

SULU3	PSTNRAGSLKDPEC	2-14	KLH	N	ND
SULU3	DPRTRASDPQSPPQVSRHK	411-429	KLH	ND	ND
PAK4	CLVPLIQLYRKQTSTC	666-680	KLH	ND	Y
PAK5	PLMRQNRTR	390-398	KLH	Y	Y
PAK5	SGDRRRAGPEKRPKSS	148-163	KLH	Y	Y
PAK5	(C) RRKSLVGTPYWMAPE	471-485	KLH	Y	ND

ND=not done yet

STE20-related protein kinase GST fusion protein immunogens and their specificity in recognizing endogenous protein by Western blots or immunoprecipitations.

Protein	domain	Aa positions	West.	IP
ZC1	Coiled-coil/pro/B/C	350-867	Y	Y
ZC1	B	615-732	Y	Y
ZC2	Coiled-coil /pro/B	348-762	ND	ND
ZC2	B	658-762	Y	Y
PAK4	Nterm	252-426	ND	ND
PAK4	Kinase/Cterm	350-681	ND	Y
PAK5	A/ Nterm	53-330	ND	ND
PAK5	A/Nterm	53-309	ND	ND

ND=not done yet

The 50kD STLK2 protein was expressed highly in several hematopoietic cell lines including Jurkat, pGL10, Ramos, A20, WEHI-231, K562, HEL and freshly isolated thymocytes from C57/BL6 mice. High levels of STLK2 expression were also detected in several tumor cell lines including Calu6, Colo205, LS180, MDAM231 and A549.

The 160 kD ZC1 protein was detected in Jurkat T cells, Colo205, HCT116, RIE-1, 293T, MDAMB231, and SK-MEL28.

The 170 kD ZC2 protein was detected in SK-Mel28 and UACC-62.

Elevated levels of the 64 kD PAK5 protein were confirmed in the breast cancer cell lines MDA-231 and MCF-7, and in the lung cancer cell line A549.

Example 5: Recombinant Expression and Biological Assays for STE20-related Protein Kinases

Materials and Methods

Transient Expression of the Ste20-related Kinases in Mammalian Cells

The pcDNA expression plasmids (10 μg DNA/100 mm plate) containing the STE20-related kinase constructs are introduced into 293 cells with lipofectamine (Gibco BRL). After 72 hours, the cells are harvested in 0.5 mL solubilization buffer (20 mM HEPES, pH 7.35, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1.5 mM $MgCl_2$, 1 mM EGTA, 2 mM phenylmethylsulfonyl fluoride, 1 μg/mL aprotinin). Sample aliquots were resolved by SDS polyacrylamide gel electrophoresis (PAGE) on 6% acrylamide/0.5% bis-acrylamide gels and electrophoretically transferred to nitrocellulose. Non-specific binding was blocked by preincubating blots in Blotto (phosphate buffered saline containing 5% w/v non-fat dried milk and 0.2% v/v nonidet P-40 (Sigma)), and recombinant protein was detected using the various anti-peptide or anti-GST-fusion specific antisera.

In Vitro Kinase Assays

Three days after transfection with the STE20-related kinase expression contructs, a 10 cm plate of 293 cells was washed with PBS and solubilized on ice with 2 mL PBSTDS containing phosphatase inhibitors (10 mM $NaHPO_4$, pH 7.25, 150 mM NaCl, 1% Triton X-100, 0.5% deoxycholate, 0.1% SDS, 0.2% sodium azide, 1 mM NaF, 1 mM EGTA, 4 mM sodium orthovanadate, 1% aprotinin, 5 μg/mL leupeptin). Cell debris was removed by centrifugation (12000 x g, 15 min, 4 °C) and the lysate was precleared by two successive incubations with 50 μL of a 1:1 slurry of protein A sepharose for 1 hour each. One-half mL of the cleared

supernatant was reacted with 10 µL of protein A purified kinase-specific antisera (generated from the GST fusion protein or antipeptide antisera) plus 50 µL of a 1:1 slurry of protein A-sepharose for 2 hr at 4 °C. The beads were then washed 2 times in PBSTDS, and 2 times in HNTG (20 mM HEPES, pH 7.5/150 mM NaCl, 0,1% Triton X-100, 10% glycerol).

The immunopurified kinases on sepharose beads were resuspended in 20 µL HNTG plus 30 mM $MgCl_2$, 10 mM $MnCl_2$, and 20 µCi [$\alpha^{32}P$]ATP (3000 Ci/mmol). The kinase reactions were run for 30 min at room temperature, and stopped by addition of HNTG supplemented with 50 mM EDTA. The samples were washed 6 times in HNTG, boiled 5 min in SDS sample buffer and analyzed by 6% SDS-PAGE followed by autoradiography. Phosphoamino acid analysis was performed by standard 2D methods on ^{32}P-labeled bands excised from the SDS-PAGE gel.

Similar assays were performed on bacterially expressed GST-fusion constructs of the kinases.

<u>ZC1 Assay buffer</u>: 20 mM Tris pH 7.4, 200 mM NaCl, 0.5 mM DTT, 3 mM MgCl2, 0.3 mM MnCl2, 100µM $^{32}P\gamma$ATP.

Substrates: myelin basic protein (MBP) at 0.28 mg/mL and phosphorylated ZC1 peptide RTVGRRNTFIG<u>T</u>-PPYWMAPE at 17 µM (bold underlined residue shows site of phosphorylation).

At higher concentrations of $MgCl_2$ (3 mM), the activity of ZC1 (both full-length and recombinant kinase domain) is up to 10-fold greater towards exogenous substrate MBP. In contrast, the autophosphorylation and the phosphorylation of the activation loop peptide substrate are both inhibited. Mn++ does not inhibit the autophosphorylation and the peptide phosphorylation by the truncated kinase domain form. However, both the MBP phosphorylation, Mn++-preferring activity AND the autophosphorylating, Mg++-preferring

activity are eliminated with mutation of the ATP-binding lysine in ZC1 (Lys54Ala) indicating that both activities are attributable to the ZC1 kinase domain.

<u>SULU1 Assay buffer</u>: This buffer is identical to that for ZC1, except for 5 mM MgCl2. Under these conditions, other STE20 family members (PAK4, ZC1) were inhibited for autophosphorylation and required reducing the [Mn] to <0.3 mM for an efficient autophosphorylation reaction.

Substrates: MBP, phosvitin, or α-casein at 0.28 mg/mL.

<u>PAK4, PAK5 Assay Buffer</u>: 20mM Hepes pH 7.2, 130 mM KCl, 10 mM MgCl2, 1 mM NaF, 20 mM B-glycerolphosphate, 0.5 mM DTT, 50 μM ATP, 0.5 μCi $^{32}P\gamma ATP$.

Substrates: MBP at 0.28 mg/mL and peptide substrates derived from PAK5 activation loop at 2.5 μM.

<u>STLK2 Assay buffer</u>: Similar to that described above, except for the inclusion of 5 mM $MgCl_2$, 5 mM $MnCl_2$ and 5 μCi $^{32}P\gamma ATP$.

<u>Transformation (PAK experiments)</u>

Low-passage NIH3T3 fibroblasts displaying normal morphology (flat, non-refractile cellular morphology), as well as low rates of spontaneous transformation, were used in transformation assays. NIH3T3 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% (v/v) fetal calf serum, penicillin (100 U/mL) and streptomycin (100 U/mL) and kept in an humidified incubator at 37 °C and 5% CO_2.

Cells were transfected with DNA-lipid complexes. As per manufacturer instructions, lipofectamine was utilized to transfect NIH3T3 cells. All transfections were with equal

amounts of plasmid DNA (DNA from the appropriate expression vector without insert was used to give equivalent amounts of DNA per transfection). 1 μg of activated allele of H-Ras was co-transfected with increasing amounts of various alleles of PAK5.

Foci were scored after 3 weeks by fixing 10 min in 10% methanol, 10% acetic acid for 10 min, followed by staining with 0.4% (w/v) crystal violet in 10% methanol for 10 min, and washing with deionized water and drying at room temperature.

Transfections, stimulations, and luciferase assays (ZC1 experiments)

Cells (10^7) were transiently transfected by electroporation using a Gene Pulser (Bio-Rad Labs) with the setting of 960 _F and 250 V. 20-40 hours later, transfected cells (about 10^5) were stimulated with various stimuli. After a 6-hour stimulation, cells were lysed, and luciferase activities were measured using the MicroLumatPlus (EG&G Berthold). (J. Exp. Med. 183:611-620, 1996, hereby incorporated by reference herein in its entirety including any drawings, tables, or figures.)

RESULTS

Protein expression and kinase activity of novel STE20-related protein kinases

Protein	Observed size (kD)	Predicted Size (kD)	In vitro Kinase activity	Endogenous Kinase activity
STLK2	50	46	y	y
STLK4	55	50	y	ND
ZC1	160	140	y	y
ZC2	170	150	y	y
KHS2	ND	101	ND	ND
SULU1	119	105	y	y
SULU3	140	115	ND	Y

PAK4	80	75	y	y
PAK5	64	64	y	y

<u>ZC1: Regulation of kinase activity</u>

ZC1 is constitutively active as a full-length kinase when expressed either *in vitro* (TNT rabbit reticulocyte system) or in NIH 3T3, 293T, or H1299 tissue culture cells. The endogenously expressed kinase is also active when immunoprecipitated from carcinoma cell lines.

<u>ZC1 signaling Pathways</u>

Using human leukemic T cell line Jurkat as a model system, the impact of cotransfected wild-type ZC1 on the activation of two reporter genes, RE/AP-luciferase and NFκB luciferase, was examined. RE/AP is a composite in the IL-2 gene promoter containing both a NFκB-like site and an AP-1 site.

Optimal activation of both RE/AP-luciferase and NFκB-luciferase reporter genes in Jurkat T cells requires signals generated from stimulation of both T cell receptor and the costimulator receptor CD28. Cotransfection of wild-type ZC1 with either the RE/AP-luciferase or the NFκB-luciferase reporter results in the activation of RE/AP or NFκB when costimulated with the anti-T cell receptor monoclonal antibody or the pharmacological reagents PMA and ionomycin that bypass proximal T cell receptor. No activation was seen when costimulated with an anti-CD28 monoclonal antibody.

These results suggest that wild-type ZC1, when overexpressed, was replacing a CD28-specific signal to activate RE/AP or NFkB. These results imply that ZC1 is involved in the CD28 signaling pathway. Since NFκB is one of the major pathways also activated by the pro-inflammatory

cytokine TNF-α signaling, it is also likely that ZC1 may be a component in the TNF-α signaling pathways.

PAK5: Design of specific peptide substrates

To aid in the development of *in vitro* kinase assays for screening small molecule libraries to identify specific inhibitors, the search for specific peptide substrates for PAK5 was undertaken.

The rationale used to design such peptides is based on the hypothesis that upon binding activated small G protein, PAK5 undergoes a conformational change that results in derepression of its kinase activity followed by autophosphorylation on the activation loop resulting in a fully active kinase. The site of autophosphorylation for related family members has been identified by biochemical and/or genetic means (e.g. Wu, C, et al. J.Biol.Chem 270:15984-15992 and Szczepanowska, et al. Proc.Natl.Acad.Sci 94, 8503-8508, 1997). Specific peptide substrates for PAK5 were designed from the sequence of the activation loop of this kinase.

An activation loop PAK5 peptide phosphorylated on the Thr residue of the TPY motif served as a high-affinity substrate for PAK5.

PAK5 activation loop peptides as kinase substrates

Peptide #	Kinase	Sequence	Aa	SEQ ID	Kinase	substrate
1	PAK5	(C)RRKSLVGTPYWMAPE	471-485	102	PAK5	yes
2	PAK5	(C)RRKSLVG**T**PYWMAPE	471-485	102	PAK5	yes
3	PAK5	(C)RRK**S**LVGTPYWMAPE	471-485	102	PAK5	no
4	KHS1	KRKSFIGTPYWMAPE	171-185	U77129	PAK5	yes
5	STLK2	KRNTFVGTPFWMAPE	175-189	5	PAK5	poor
6	SULU1	PANSFVGTPYWMAPE	174-188	22	PAK5	poor
7	ZC1	RRNTFIGTPYWMAPE	184-198	13	PAK5	poor
8	ZC1	RRNTFIG**T**PYWMAPE	184-198	13	PAK5	poor
9	STLK4	RNKVRKTFVGTPCWMAPE	66-83	7	PAK5	poor
10	PAK5	(C)RRKSLVG**T**PYWMAPE	471-485	102	PAK4	yes

Note: underlined/ bold reside was phosphorylated

Peptide #	Kinase	Notes
1	PAK5	Equally well as MBB
2	PAK5	High Km for PAK5 (1-10 μM)
3	PAK5	S is the site of phosphorylation
4	KHS1	Similar to peptide 1
5	STLK2	
6	SULU1	
7	ZC1	
8	ZC1	Better than 7
9	STLK4	
10	PAK5	Same Km as phosph. by PAK5

PAK5: Transformation

Transformation of low-passage NIH3T3 cells by ras in the presence or absence of various alleles of PAK5 showed that the dominant negative, kinase-dead allele of PAK5 was able to block ras transformation of NIH3T3 cells. Thus, PAK5 activity is required for ras transformation of NIH3T3 cells. Inhibition of PAK5 activity may have therapeutic value as an anti-proliferative agent for treating cancer.

PAK4 and PAK5: interaction with Cdc42

PAK 4 interacts with CDC42 small G-protein but not Rac, RhoA, or Ras as determined by co-transfection of recombinant genes and detection by kinase assays. PAK5 also interacts with Cdc42. Coding sequences of activated alleles of small G proteins (ras, Cdc42, Rac, Rho) tagged with a Myc epitope were transiently expressed in 293T cells, various alleles of 35S-labeled PAK5 tagged with HA epitope were expressed *in vitro* with the reticulocyte (TNT) system.

Example 6: Chromosomal Localization of Ste20-Related Protein Kinases

Materials And Methods

STE20 protein kinases STLK3, STLK4, ZC1, ZC2, ZC3, KHS2, SULU1, PAK4, and PAK5 were mapped using the GeneBridge 4 Radiation Hybrid Panel, RH02.05 (Research Genetics). The GeneBridge 4 Panel consists of 91 hybrid panel samples, in addition to one human positive control (HFL), and one hamster negative control (A23). The standard reaction conditions used to test and conduct PCR reactions using the GeneBridge 4 Panel are available from Research Genetics.

Oligonucleotide sequences (all 5' to 3') used for PCR mapping were:

STLK3:	CTCCCATTTCCTAGCAAAATCA,	AGAGGCAGTATTGTCAGATGTA
STLK4:	CCACACATGCGTATCTCTGTTG,	TTGCTAGAATTCACATCAGGTACA
ZC1:	ATCCCTGGATCACACTGCTTCT,	CAAGGTGTTCTTTGCCTCTGTT
ZC2:	AGATGGACTGTACTGGGAGGG,	AGAAGAGCACTTGGCACTTATC
ZC3:	CATCATGAACTGGTGACGGG,	CCAGTGAAATCAAACCAGTAAAA
SULU1:	CAAAACCTGGCCGTCTCTTCTATT,	ATTTGTGCTACTGGGATTCTGTG
KHS2:	GAATAGCGGTACCATGATAGAATA,	TACCAAAAAGAGCCAAAAGTGTG
PAK4:	CTCAGTATTCTCTCCAAAGATTG,	GATGTTCTCTCCATTCTGTAAAG
PAK5:	CATCACTGGAAGTCTGCAGTG,	CAGGTGCAGTAGTCATTTGC

Positive reactions were assigned a score of "1", negative reactions are assigned a score of "0", and ambiguous reactions are assigned a score of "2". Results were submitted to the Whitehead Institute (www@genome.wi.mit.edu) for position analysis. Chromosomal localizations for ZC4, SULU3, STLK2, STLK5 and STLK6 were available publicly (for example, from Unigene). The chromosomal locations of GEK2 and STLK7 have not been determined.

STLK2_h	Xq25-27.1	(Public)
STLK3	2q31.3	(Sugen)
STLK4_h	3p22.3-p22.2	(Sugen)
STLK5_h	17q23.2-24.2	(Public)

STLK6_h	2q32.2 -q33.3	(Public)
STLK7_h	NA	
ZC1_h	2p11.2	(Sugen)
ZC2_h	3q26.31-3q26.32	(Sugen)
ZC3_h	17p13.2-13.3	(Sugen)
ZC4_h	Xq22	(Public)
KHS2_h	2p22-2p22.2	(Sugen)
SULU1_h	12q24.21	(Sugen)
SULU3_h	17p11.2	(Public)
GEK2_h	NA	
PAK4_h	15q14	(Sugen)
PAK5_h	19q13.2-q13.3	(Sugen)

Many of the STE 20 kinases were mapped to regions associated with various human cancers, as shown below.

The regions were also cross-checked with the Mendalian Inheritance in Man database, which tracks genetic information for many human diseases, including cancer. References for association of the mapped sites with chromosomal abnormalities found in human cancer can be found in: Knuutila, et al., Am J Pathol, 1998, 152:1107-1123, hereby incorporated herein be reference in its entirety including any figures, tables, or drawings. Association of these mapped regions with other diseases is documented in the Online Mendalian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/htbin-post/Omim).

STLK2_h, Xq25-27.1, (Public)
Osteosarcoma, Xq25-qter, 2 of 31.
Lymphoproliferative syndrome, X-linked (OMIM No. 308240)
human STLK3, 2q31.3, (Sugen)
Squamous cell carcinoma of Head and Neck, 3 of 30.

STLK4_h, 3p22.3-p22.2, (Sugen)
Mantle cell lymphoma 3p14-p22 1 of 27
Squamous cell carcinoma of Head and Neck 3p22-p24 1 of 14
Cardiomyopathy, dilated (OMIM 601154)

STLK5_h, 17q23.2-24.2, (Public)
Cervical cancer, 17q, 1 of 30
Gastroesophageal junction adenocarcinoma xenograft, 17q, 1 of 5
Breast carcinoma, 17q12-qter, 1 of 16
Bladder carcinoma, 17q22-q23, 1 of 14
Breast carcinoma, 17q22-q25, 8 of 101
Non-small cell lung cancer, 17q24-q25, 6 of 50
Testis, 17q24-qter, 2 of 11
Malignant peripheral nerve sheath tumors, 17q24-qter, 5 of 7
Alzheimer disease, susceptibility to (OMIM 106180)

STLK6_h, 2q32.2 -q33.3, (Public)
Non-small cell lung cancer, 2q31-q32, 1 of 50
Squamous cell carcinoma of Head and Neck, 2q31-q33, 3 of 30
Small cell lung cancer, 2q32-q35, 1 of 22

ZC1_h, 2p11.2, (Sugen)
non-small cell lung cancer, 2pter-q13, 1 of 10
non-small cell lung cancer, 2pter-q21, 1 of 10
Pulmonary alveolar proteinosis, congenital (OMIM 178640).

ZC2_h, 3q26.31-3q26.32, (Sugen)
Non-small cell lung cancer, 3q26.1-q26.3, 26 of 103
Cervical cancer, 3q26.1-q27, 4 of 30
Small cell lung cancer, 3q26.3-qter, 3 of 35
Squamous cell carcinoma of Head and Neck, 3q26.3-qter, 3 of 13
Marginal zone B-cell lymphoma, 3q26-q27, 1 of 25
Parosteal osteosarcoma, 3q26-q28, 1 of 1
Gastrointestinal stromal tumor, 3q26-q29, 1 of 16
Mantle cell lymphoma, 3q26-q29, 1 of 5

<u>ZC3_h</u> 17p13.2-13.3 (Sugen)
Malignant fibrous histiocytoma of soft tissue, 17p, 2 of 58
Leiomyosarcoma, 17p, 7 of 29
Non-small cell lung cancer, 17p, 1 of 50

<u>ZC4_h</u>, Xq22, (Public)
Diffuse large cell lymphoma, Xq22-ter, 1 of 32
Deafness, X-linked 1, progressive. (OMIM 304700).

<u>KHS2_h</u>, 2p22-2p22.2, (Sugen)
Synovial sarcoma, 2p21-q14, 1_of_67
Follicular lymphoma, 2p22-p24, 1_of_46
Colorectal cancer, hereditary, nonpolyposis, type 1, Ovarian cancer (MSH2, COCA1, FCC1). (OMIM 120435).

<u>SULU1_h</u>, 12q24.21 (Sugen)
Neuroglial tumors, 12q22-qter, 1_of_15
Gastroesophageal junction adenocarcinoma, 12q23-qter, 1 of 5.
Non-small cell lung cancer, 12q24.1-24.3, 2 of 50.

<u>SULU3_h</u> 17p11.2 (Public)
Malignant fibrous histiocytoma of soft tissue, 17p, 2_of_58
Leiomyosarcoma, 17p, 7_of_29
non-small cell lung cancer, 17p, 1_of_50
Diffuse large cell lymphoma, 17p11.2, 1_of_32
Osteosarcoma, 17p11.2-p12, 4_of_31

<u>PAK4_h</u>: 15q14 (Sugen)
Schizophrenia, (OMIM 118511).

PAK5_h: 19q13.2-q13.3 (Sugen)

Follicular lymphoma, 19q13, 1 of 46*

Mantle cell lymphoma, 19q13, 1 of 5

Hepatocellular carcinoma, 19q13.1, 2 of 50

Small cell lung cancer, 19q13.1, 10 of 35

Breast carcinoma, 19q13.1-qter, 1 of 33

cervical cancer, 19q13.1-qter, 1 of 30

Testis, 19q13.1-qter, 1 of 11

Chondrosarcoma, 19q13.2, 1 of 29

Malignant fibrous histiocytoma of soft tissue, 19q13.2-qter, 2 of 58

Non-small cell lung cancer, 19qcen-q13.3, 6 of 104

Example 7: Demonstration Of Gene Amplification By Southern Blotting

Materials and Methods

Nylon membranes were purchased from Boehringer Mannheim. Denaturing solution contains 0.4 M NaOH and 0.6 M NaCl. Neutralization solution contains 0.5 M Tris-HCL, pH 7.5 and 1.5 M NaCl. Hybridization solution contains 50% formamide, 6X SSPE, 2.5X Denhardt's solution, 0.2 mg/mL denatured salmon DNA, 0.1 mg/mL yeast tRNA, and 0.2 % sodium dodecyl sulfate. Restriction enzymes were purchased from Boehringer Mannheim. Radiolabeled probes were prepared using the Prime-it II kit by Stratagene. The beta actin DNA fragment used for a probe template was purchased from Clontech.

Genomic DNA was isolated from 20 different tumor cell lines: MCF-7, MDA-MB-231, Calu-6, A549, HCT-15, HT-29, Colo 205, LS-180, DLD-1, HCT-116, PC3, CAPAN-2, MIA-PaCa-2, PANC-1, AsPc-1, BxPC-3, OVCAR-3, SKOV3, SW 626 and PA-1, and from two normal cell lines: human mammary epithelial cells and human umbilical vein endothelial cells.

A 10 μg aliquot of each genomic DNA sample was digested with EcoR I restriction enzyme and a separate 10 μg sample was digested with Hind III restriction enzyme. The restriction-digested DNA samples were loaded onto a 0.7% agarose gel and, following electrophoretic separation, the DNA was capillary-transferred to a nylon membrane by standard methods (Sambrook, J. et al (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory).

PAK5 Amplicon:

A 600 base pair fragment (EcoR I - Sac I) of the PAK5 gene was used as a template for a radiolabeled DNA probe which was hybridized to the blots at 42 °C for 48 hours in hybridization solution using standard methods (supra). The blots were exposed to a phosphorimager screen for 4 days, then scanned and analyzed using a Molecular Dynamics Storm 840 phosphorimager. The relative mass and gene copy number values of the PAK5 DNA fragments were calculated from the band density values obtained. The blots were re-hybridized with a radiolabeled probe copied from a fragment of human beta actin DNA and developed as above to confirm the sample mass loading equivalency.

RESULTS

The PAK5 gene was determined to exhibit 3-fold amplification compared to the normal DNA copy number in PANC-1 (pancreatic epithelioid carcinoma) and OVCAR-3 (ovarian adenocarcinoma) human cell lines, and approximately 2 times the normal copy number in the BxPC-3 (primary pancreatic adenocarcinoma) human cell line.

Similar Southern analyses can be performed for other STE20 kinases.

Example 8: Detection Of Protein-Protein Interaction Through Phage Display

Materials And Methods

Phage display provides a method for isolating molecular interactions based on affinity for a desired bait. cDNA fragments cloned as fusions to phage coat proteins are displayed on the surface of the phage. Phage(s) interacting with a bait are enriched by affinity purification and the insert DNA from individual clones is analyzed.

T7 Phage Display Libraries

All libraries were constructed in the T7Select1-1b vector (Novagen) according to the manufacturer's directions.

Bait Presentation

Protein domains to be used as baits were generated as C-terminal fusions to GST and expressed in *E. coli*. Peptides were chemically synthesized and biotinylated at the N-terminus using a long chain spacer biotin reagent.

Selection

Aliquots of refreshed libraries (10^{10}-10^{12} pfu) supplemented with PanMix and a cocktail of *E. coli* inhibitors (Sigma P-8465) were incubated for 1-2 hrs at room temperature with the immobilized baits. Unbound phage was extensively washed (at least 4 times) with wash buffer.

After 3-4 rounds of selection, bound phage was eluted in 100 µL of 1% SDS and plated on agarose plates to obtain single plaques.

Identification of insert DNAs

Individual plaques were picked into 25 µL of 10 mM EDTA and the phage was disrupted by heating at 70 °C for 10 min.

2 µL of the disrupted phage were added to 50 µL PCR reaction mix. The insert DNA was amplified by 35 rounds of thermal cycling (94oC, 50sec; 50oC, 1min; 72oC, 1min).

Composition of Buffer

10x PanMix

5% Triton X100

10% non-fat dry milk (Carnation)

10 mM EGTA

250 mM NaF

250 µg/mL Heparin (sigma)

250 µg/mL sheared, boiled salmon sperm DNA (sigma)

0.05% Na azide

Prepared in PBS

Wash Buffer

PBS supplemented with:

0.5% NP-40

25 µl g/mL heparin

PCR reaction mix

1.0 mL	10x PCR buffer (Perkin-Elmer, with 15 mM Mg)
0.2 mL each	dNTPs (10 mM stock)
0.1 mL	T7UP primer (15 pmol/µL) GGAGCTGTCGTATTCCAGTC
0.1 mL	T7DN primer (15 pmol/µL) AACCCCTCAAGACCCGTTTAG
0.2 mL	25 mM $MgCl_2$ or $MgSO_4$ to compensate for EDTA

Q.S. to 10 mL with distilled water

Add 1 unit of Taq polymerase per 50 µL reaction

LIBRARY: T7 Select1-H441

RESULTS

Phage display baits and interactors

Bait	Domain	Aa	Patent SEQ ID	CDNA library	Interactor	Sequence Range & SEQ ID
SULU1	Coiled-coil2	752-898	22	H441	GEK2 cc dom (1)	677-820 SEQ #26
SULU3	Coiled-coil2	755-898	23	H441	SLK isoform	M83780

(1) SULU1 cc1 also interacted to a lesser extent with the coiled-coil domain of an SLK isoform.

The phage display data suggest potential interactions of SULU3 with SLK and SULU1 with GEK2 through their coiled-coil domains. Therefore two members of the SULU subfamily of STE20 kinases interact with two members of a separate STE20 family, the prototype being SLK.

These results suggest a specificity in the interaction, and imply that these STE20 kinases may interact with each other through homo- and hetero-dimerization. Alternatively SULU-related kinases could act immediately up- or down-stream of the SLK-related kinases in a signaling cascade.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The molecular complexes and the methods, procedures, treatments, molecules, specific compounds described herein are presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to

the invention disclosed herein without departing from the scope and spirit of the invention.

All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

In particular, although some formulations described herein have been identified by the excipients added to the formulations, the invention is meant to also cover the final formulation formed by the combination of these excipients. Specifically, the invention includes formulations in which one to all of the added excipients undergo a reaction during formulation and are no longer present in the final formulation, or are present in modified forms.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine,

chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described.

Other embodiments are within the following claims.

What is claimed is:

CLAIMS

1. An isolated, enriched, or purified nucleic acid molecule encoding a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

2. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule comprises a nucleotide sequence that:

(a) encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, or SEQ ID NO:107;

(b) is the complement of the nucleotide sequence of (a);

(c) hybridizes under highly stringent conditions to the nucleotide molecule of (a) and encodes a naturally occurring kinase polypeptide;

(d) encodes a kinase polypeptide having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, or SEQ ID NO:107, except that it lacks one or more, but not all, of the following segments of amino acid residues: 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489 or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 1-22, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID

NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 282-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID NO:103, or 1-33, 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107;

(e) is the complement of the nucleotide sequence of (d);

(f) encodes a polypeptide having the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, or SEQ ID NO:107 from amino acid residues 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489 or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 282-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID

NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID NO:103, or 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107;

(g) is the complement of the nucleotide sequence of (f);

(h) encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, or SEQ ID NO:107, except that it lacks one or more, but not all, of the domains selected from the group consisting of a C-terminal domain, a catalytic domain, an N-terminal domain, a spacer region, a proline-rich region, a coiled-coil structure region, and a C-terminal tail; or

(i) is the complement of the nucleotide sequence of (h).

3. The nucleic acid molecule of claim 1, further comprising a vector or promoter effective to initiate transcription in a host cell.

4. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule is isolated, enriched, or purified from a mammal.

5. The nucleic acid molecule of claim 4, wherein said mammal is a human.

6. A nucleic acid probe for the detection of nucleic acid encoding a kinase polypeptide in a sample, wherein said polypeptide is selected from the group consisting of STLK2,

STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

7. The probe of claim 6, wherein said polypeptide is a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, or SEQ ID NO:107.

8. A recombinant cell comprising a nucleic acid molecule encoding a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

9. The cell of claim 8, wherein said polypeptide is a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, or SEQ ID NO:107.

10. An isolated, enriched, or purified kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

11. The polypeptide of claim 10, wherein said polypeptide is a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6,

SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107.

12. The polypeptide of claim 10, wherein said polypeptide comprises:

(a) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107;

(b) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, except that it lacks one or more, but not all, of the following segments of amino acid residues: 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489 or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 1-22, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 282-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ

ID NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID NO:103, 1-24, 25-289, 290-397, 398-628, 629-668, 669-872, or 873-1227 of SEQ ID NO:105, or 1-33, 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107;

(c) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107 from amino acid residues 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489, or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 282-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID NO:103, 1-24, 25-289, 290-397, 398-628, 629-668, 669-872, or 873-1227 of SEQ ID NO:105, or 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107; or

(d) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, except that it

lacks one or more, but not all, of the domains selected from the group consisting of a C-terminal domain, a catalytic domain, an N-terminal domain, a spacer region, a proline-rich region, a coiled-coil structure region, and a C-terminal tail.

13. The kinase polypeptide of claim 10, wherein said polypeptide is isolated, purified, or enriched from a mammal.

14. The kinase polypeptide of claim 13, wherein said mammal is a human.

15. The kinase polypeptide of claim 10, wherein said polypeptide is a STLK2, STLK3, STLK4, STLK5, STLK6, STLK7 polypeptide.

16. The kinase polypeptide of claim 10, wherein said polypeptide is a ZC1, ZC2, ZC3, or ZC4 polypeptide.

17. The kinase polypeptide of claim 10, wherein said polypeptide is a KHS2 polypeptide.

18. The kinase polypeptide of claim 10, wherein said polypeptide is a SULU1 or SULU3 polypeptide.

19. The kinase polypeptide of claim 10, wherein said polypeptide is a GEK2 polypeptide.

20. The kinase polypeptide of claim 10, wherein said polypeptide is a PAK4 or PAK5 polypeptide.

21. An antibody or antibody fragment having specific binding affinity to a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5 or a kinase domain polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

22. A hybridoma which produces an antibody having specific binding affinity to a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

23. A method for identifying a substance that modulates kinase activity comprising the steps of:

(a) contacting a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5 with a test substance;

(b) measuring the activity of said polypeptide; and

(c) determining whether said substance modulates the activity of said polypeptide.

24. A method for identifying a substance that modulates kinase activity in a cell comprising the steps of:

(a) expressing a kinase polypeptide in a cell, wherein said polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5;

(b) adding a test substance to said cell; and

(c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

25. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a kinase selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

26. The method of claim 25, wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer.

27. The method of claim 25, wherein said substance modulates kinase activity *in vitro*.

28. The method of claim 27, wherein said substance is a kinase inhibitor.

29. A method for detection of a kinase polypeptide in a sample as a diagnostic tool for a disease or disorder, wherein said method comprises:

(a) contacting said sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a nucleic acid target region of a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, said probe comprising the nucleic acid

sequence encoding said polypeptide, fragments thereof, or the complements of said sequences and fragments; and

(b) detecting the presence or amount of the probe:target region hybrid as an indication of said disease.

30. The method of claim 29, wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer.

31. A method for detection of a kinase polypeptide in a sample as a diagnostic tool for a disease or disorder, wherein said method comprises:

(a) comparing a nucleic acid target region encoding said kinase polypeptide in a sample, wherein said kinase polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, or one or more fragments thereof, with a control nucleic acid target region encoding said kinase polypeptide, or one or more fragments thereof; and

(b) detecting differences in sequence or amount between said target region and said control target region, as an indication of said disease or disorder.

32. The method of claim 31, wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer.

```
STE20_h  ----------MAHLRGFANQHSRV----DPEELFTKLDRIGKGSFGEVYKGIDNHTK  43
MST3_h   ----------MAHSPVQSGLPGMQNLKADPEELFTKLEKIGKGSFGEVFKGIDNRTQ  47
STLK2_h  ----------MAHSPVAVQVPGMQNNIADPEELFTKLERIGKGSFGEVFKGIDNRTQ  47
STLK3_h  TAAPAPAAPAAPAPAPAPAPAAQAVGWPICRDAYELQEVIGSGATAVVQAALCKPRQ  57

STE20_h  EVVAIKIIDLEEAEDEIEDIQQEITVLSQCDSPYITRYFGSYLKSTKLWIIMEYLGG  100
MST3_h   KVVAIKIIDLEEAEDEIEDIQQEITVLSQCDSPYVTKYYGSYLKDTKLWIIMEYLGG  104
STLK2_h  QVVAIKIIDLEEAEDEIEDIQQEITVLSQCDSSYVTKYYGSYLKGSKLWIIMEYLGG  104
STLK3_h  ERVAIKRINLEKCQTSMDELLKEIQAMSQCSHPNVVTYYTSFVVKDELWLVMKLLSG  114

STE20_h  GSALDLLKPGP---------LEETYIATILREILKGLDYLHSERKIHRDIKAANVLL  148
MST3_h   GSALDLLEPGP---------LDETQIATILREILKGLDYLHSEKKIHRDIKAANVLL  152
STLK2_h  GSALDLLRAGP---------FDEFQIATMLKEILKGLDYLHSEKKIHRDIKAANVLL  152
STLK3_h  GSMLDIIKYIVNRGEHKNGVLEEAIIATILKEVLEGLDYLHRNGQIHRDLKAGNILL  171
STLK4_h  ----------------KSGVLDXSTIATILREVLEGLEYLHKXGQIHRDVKAGNILX  41

STE20_h  SEQGDVKLADFGV-A-----GQLTDTQIKRNTFVGTPFWMAPEVIKQSA-YDFKADI  198
MST3_h   SEHGEVKLADFGV-A-----GQLTDTQIKRNTFVGTPFWMAPEVIKQSA-YDSKADI  202
STLK2_h  SEQGDVKLADFGV-A-----GQLTDTQIKRNTFVGTPFWMAPEVIQQSA-YDSKADI  202
STLK3_h  GEDGSVQIADFGVSAFLATGGDVTRNKV-RKTFVGTPCWMAPEVMEQVRGYDFKADM  227
STLK4_h  GEDGSVQIADFGVSAFLATGGDITRNKV-RKTFVGTPCWMAPEVMEQVRGYDFKADI  97
```

Fig. 1A

SUBSTITUTE SHEET (RULE 26)

```
STE20_h  WSLGITAIELAKGEPPNSDLHPMRVLFLIPKNSPPTLE-G--------QHSKPFKEF 246
MST3_h   WSLGITAIELARGEPPHSELHPMKVLFLIPKNNPPTLE-G--------NYSKPLKEF 250
STLK2_h  WSLGITAIELAKGEPPNSDMHPMRVLFLIPKNNPPTLV-G--------DFTKSFKEF 250
STLK3_h  WSFGITAIELATGAAPYHKYPPMKVLMLTLQNDPPTLETGVEDKEMMKKYGKSFRKL 284
STLK4_h  WSFGITAIELATGAAPYHKYPPMKVLMLTLQNDPPSLETGVQDKEMLKKYGKSFRKM 154

STE20_h  VEACLNKDPRFRPTAKELLKHKFITRYTKKTSFLTELIDRYKR-------------- 289
MST3_h   VEACLNKEPSFRPTAKELLKHKFILRNAKKTSYLTELIDRYKR-------------- 293
STLK2_h  IDACLNKDPSFRPTAKELLKHKFIVKNSKKTSYLTELIDRFKR-------------- 293
STLK3_h  LSLCLQKDPSKRPTAAELLKCKFFQKAKNREYLIEKLLTRTPDIAQRAKKVRRVPGS 341
STLK4_h  ISLCLQKDPEKRPTAAELLRHKFFQKAKNKEFLQEKTLQRAPTISERAKKVRRVPGS 211

STE20_h  -----------WKSEGHGEESS-SEDSDIDGEAEDGEQGPIW--------------- 319
MST3_h   -----------WKAEQSHDDSS-SEDSDAETDGQASGGSDSG--------------- 323
STLK2_h  -----------WKAEGHSDDESDSEGSDSESTSRENNTHPEW--------------- 324
STLK3_h  SGHLHKTEDGDWEWSDDEMDEK-SEEGKAAFSQEKSRRVKEE--------------- 382
STLK4_h  SGRLHKTEDGGWEWSDDEFDEE-SEEGKAAISQLRSPRVKESISNSELFPTTDPVGT 267

STE20_h  --------------------------TFPPTIRPSPHSKLHKGTALHSSQKPAEPVK 350
MST3_h   --------------------------DWIFTIREKDPKNLENGALQPSDLDRNKMKD 354
STLK2_h  --------------------------SFTTVRKKPDPKKVQNGAEQDLVQTLS---- 351
STLK3_h  --------------------------NPEIAVSASTIPEQIQSLSVHDSQGPPNANE 413
STLK4_h  LLQVPEQISAHLPQPAGQIATQPTQVSLPPTAEPAKTAQALSSGSGSQETKIP---- 320
```

Fig. 1B

```
STE20_h   RQ--PRSQCLSTLVRPVFGELKEKHKQSGGSVGALEELENAFSLAEESCPGISDKLM  405
MST3_h    IPKRPFSQCLSTIISPLFAELKEKSQACGGNLGSIEELRGAIYLAEEACPGISDTMV  411
STLK2_h   --------CLSMIITPAFAELKQQDENNASRNQAIEELEKSIAVAEAACPGITDKMV  400
STLK3_h   DY--REASSCAVNLVLRLRNSRKELNDIRFEFTPGRDTADGVSQELFSAGLVDGHDV  468
STLK4_h   ------------ISLVLRLRNSKKELNDIRFEFTPGRDTAEGVSQELISAGLVDGRDL  366

STE20_h   VHLVERVQRFSHNRNHLTSTR                                      426
MST3_h    AQLVQRLQRYSLSGGGTSSH                                       431
STLK2_h   KKLIEKFQKCSADESP                                           416
STLK3_h   VIVAANLQKIVDDPKALKTLTFKLASGCDGSEIPDEVKLIGFAQLSVS          516
STLK4_h   VIVAANLQKIVEEPQSNRSVTFKLASGVEGSDIPDDGKLIGFAQLSIS          414
```

Fig. 1C

```
Ste20_h     MAHLRGFANQHSRV---------------DPEELFTKLDRIGKGSFGEVYKGIDNHTK  43
T19A5.2_ce  MTTTSSDELPRQADDDSMKWDRIYIQKLDPEVIFTKQERIGRGSFGEVYKGIDNRTG  57
Pak_sp      ---------------------------LLYRNFVKIGQGASGDVYSARQVGTN  26
STLK5_h     -----------------------------------------------------------  0

Ste20_h     EVVAIKIIDLEEAEDEIEDIQQEITVLSQCDSPYITRYFGSYLKSTKLWIIMEYLGG  100
T19A5.2_ce  RVVAIKIIDLEQAEDEIEDIQQEIQVLSQCDSQYVTKYFGSFLKGSKLWIIMEYLGG  114
Pak_sp      LSVAIKKMNINQQPKKEF-IVNEILVMKSHHHKNIVNFIDTFFYKSELWMVMEYMRG  82
STLK5_h     -----------------------------------------------------------  0

Ste20_h     GSALDLLKPGPLEETYIATILREILKGLDYLHSERKIHRDIKAANVLLSEQGDVKLA  157
T19A5.2_ce  GSALDLTKSGKLDESHIAVILREILKGLEYLHSERKIHRDIKAANVLVSEHGDVKVA  171
Pak_sp      GSLTEVVTNNTLSEGQIAAICKETLEGLQHLHENGIVHRDIKSDNILLSLQGDIKLT  139
STLK5_h     --LICTHFMDGMNELAIAYILQGVLKALDYIHHMGYVHRSVKASHILISVDGKVYLS  55

Ste20_h     DFGVAGQLTDTQIKRNTFVGTPF-------WMAPEVIKQSA--YDFKADIWSLGITA  205
T19A5.2_ce  DFGVAGQLTETVKKRITFVGSPF-------WMAPELIKQSS--YDYKADIWSLGITA  219
Pak_sp      DFGFCAQIDSNMTKRTTMVGTPY-------WMAPEVVTRKE--YGFKVDVWSLGIMA  187
STLK5_h     GLRSNLSMISAGQRQRVVHDFPKYSVKVLPWLSPEVLQQNLQGYDAKSDIYSVGITA  112

Ste20_h     IELAKGEPPNSDLHPMRVLFLIPK-NSPPTLEG-Q----------------------  238
T19A5.2_ce  IELANGEPPHSDLHPMRVLFLIPK-NPPPVLQGSQ----------------------  253
Pak_sp      IEMVEGEPPYLNENPLRALYLIATIGTPKISRPEL----------------------  222
STLK5_h     CELANGHVPFKDMPATQMLLEKLN-GTVPCLLD-TSTIPAEELTMSPSRSVANSGLS  167
```

Fig. 2A

```
Ste20_h      -----------------------HSKPFKEFVEACLNKDPRFRPTAKELLKHKFITR 272
T19A5.2_ce   -----------------------WSKPFKEFVEMCLNKDPENRPSASTLLKHQFIKR 287
Pak_sp       -----------------------LSSVFHDFLSKSLTVNPKQRPSSGELLRHPFLKQ 256
STLK5_h      DSLTTSTPRPSNGDSPSHPYHRTFSPHFHHFVEQCLQRNPDARPSASTLLNHSFFKQ 224

Ste20_h      YTKKTSFLTELIDRYKRWKSEGHGEESSSEDSDIDGEAEDGEQGPIWTFPPTIRPSP 329
T19A5.2_ce   AKKNS-----ILVDLIERAAEYRLRTGVSSDSDLDEDSDGGGGTSKWDY-PTVRGPR 338
Pak_sp       AVPVS-----SLIPLIKSIHHSGK                                  275
STLK5_h      --------------------------------------------------------- 224

Ste20_h      HSKLHKGTALHSSQKPAEPVKRQPRSQCLSTLVRPV-----FGELKEKHKQSG--GS 379
T19A5.2_ce   VSADDDGTVRQRTDRPRAQVDRRSPSGSPGGTIVRG-----SPQVAAVAEQLR--NS 388
STLK5_h      -------------------IKRRA-SEALPELLRPVTPITNF-EGSQSQDHSGIFGL 260

Ste20_h      VGALEELENAFSLAEESCPGISDKLMVHLVERVQRFSHNRNHLTSTR           426
T19A5.2_ce   XXALDQLRHVFRDVEDSCPGICNELIEELMQRIAVPQVSQSDLDAAIRRLTTPPS   443
STLK5_h      VTNLEELEVDDWEF                                            274
```

Fig. 2B

```
ZC504.4_ce  MSSSGEDE----IDLNSLRDPAGIFELIEVVGNGTYGQVYKGRHVKTAQLAAIKIMNINE  58
NIK_m       MANDSPAKSLVDIDLSSLRDPAGIFELVEVVGNGTYGQVYKGRHVKTVT-AAIKVMDVTE  69
ZC1_h       MANDSPAKSLVDIDLSSLRDPAGIFELVEVVGNGTYGQVHEGRHVKTGQLAAIKVMDVTE  60
ZC2_h       ----------------------------------AFGEVYEGRHVKTGQLAAIKVMDVTG  28
ZC3_h       ----------------------------------AFGEVYEGRHVKTGQLAAIKVMDVTE  28

ZC504.4_ce  DEEDEIKLEINMLKKHSHHRNVATYYGAFIKKLPSSTGKHDQLWLVMEFCGSGSITDLVK  116
NIK_m       DEEEEITLEINMLKKYSHHRNIATYYGAFIKKSPPGHD--DQLWLVMEFCGAGSITDLVK  117
ZC1_h       DEEEEIKLEINMLKKYSHHRNIATYYGAFIKKSPPGHD--DQLWLVMEFCGAGSITDLVK  118
ZC2_h       DEEEEIKQEINMLKKYSHHRNIATYYGAFIKKNPPGMD--DQLWLVMEFCGAGSVTDLIK  84
ZC3_h       DEEEEIKQEINMLKKYSHHRNIATYYGAFIKKSPPGND--DQLWLVMEFCGAGSVTDLVK  84

ZC504.4_ce  NTKGGSLKEEWIAYICREILRGLYHLHQSKVIHRDIKGQNVLLTDSAEVKLVDFGVSAQL  176
NIK_m       NTKGNTLKEDWIAYISREILRGLAHLHIHHVIHRDIKGQNVLLTENAEVKLVDFGVSAQL  177
ZC1_h       NTKGNTLKEDWIAYISREILRGLAHLHIHHVIHRDIKGQNVLLTENAEVKLVDFGVSAQL  178
ZC2_h       NTKGNTLKEEWIAYICREILRGLSHLHQHKVIHRDIKGQNVLLTENAEVKLVDFGVSAQL  144
ZC3_h       NTKGNALKEDCIAYICREILRGLAHLHAHKVIHRDIKGQNVLLTENAEVKLVDFGVSAQL  144

ZC504.4_ce  DKTVGRRNTFIGTPYWMAPEVIACDESPEATYDSRSDLWSLGITALEMAEGHPPLCDMHP  236
NIK_m       DRTVGRRNTFIGTPYWMAPEVIACDENPDATYDYRSDLWSCGITAIEMAEGGPPLCDMHP  237
ZC1_h       DRTVGRRNTFIGTPYWMAPEVIACDENPDATYDYRSDLWSCGITAIEMAEGAPPLCDMHP  238
ZC2_h       DRTVGRRNTFIGTPYWMAPEVIACDENPDATYDFKSDLWSLGITAIEMAEGAPPLCDMHP  204
ZC3_h       DRTVGRRNTFIGTPYWMAPEVIACDENPDATYDYRSDTWSLGITAIEMAEGAPPLCDMHP  204
```

Fig. 3A

```
ZC504.4_ce  MRALFLIPRNPPPKLKRNKKWTKKFETFIETVLVKDYHQRPYTGALLRHPFIKEQPHEQT 296
NIK_m       MRALFLIPRNPPPRLK-SKKWSKKFFSFIEGCLVKNYMQRPSTEQLLKHPFIRDQPNERQ 296
ZC1_h       MRALFLIPRNPPPRLK-SKKWSKKFFSFIEGCLVKNYMQRPSTEQLLKHPFIRDQPNERQ 297
ZC2_h       MRALFLIPRNPAPRLK-SKKWSKKFQSFIESCLVKNHSQRPATEQLMKHPFIRDQPNERQ 263
ZC3_h       MRALFLIPRNPPPRLK-SKKWSKKFTDFIDTCLIKTYLSRPPTEQLLKFPFIRDQPTERQ 263

ZC504.4_ce  IRHSIKEHIDRNRRVKKQDADYEYSGSEDDEPSPNNRDDSESS---SMIPMDNTLRKGFQ 353
NIK_m       VRIQLKDHIDRTRKKRGEKDETEYEYSGSEEEEEEVPEQEGEPSSIVNVPGESTLRRDFL 356
ZC1_h       VRIQLKDHIDRTRKKRGEKDETEYEYSGSEEEEEEVPEQEGEPSSIVNVPGESTLRRDFL 357
ZC2_h       VRIQLKDHIDRTKKKRGEKDETEYEYSGSEEEEEE--NDSGEPSSILNLPRESTLRRDFL 321
ZC3_h       VRIQLKDHIDRSRKKRGEKEETEYEYSGS-EEEDDSHGEEGEPSSIMNVPGESTLRREFL 322

ZC504.4_ce  KLQESSRGFAEPGAQQLRRLPQQPAPAPFQYQQSRYVEPRRESSEVKLRAVSSRGAADGP 413
NIK_m       RLQQENKERSEALRRQQLLQEQQL----------------REQEEYKRQLLAERQKRI-- 398
ZC1_h       RLQQENKERSEALRRQQLLQEQQL----------------REQEEYKRQLLAERQKRI-- 399
ZC2_h       RLQLANKERSEALRRQQ--LEQQQ----------------RENEEHKRQLLAERQKRI-- 361
ZC3_h       RLQQENKSNSEALKQQQQLQQQQQ----------------RQPEAHIKHLLHQRQRRI-- 364

ZC504.4_ce  RHSPASRPRPRSPQQSHPAAPHLADLANYEKRRRSEREERRERERQAHHAMPIARVSASV 473
NIK_m       EQQKEQRRRLEEQQRREREARRQQEREQRRREQEEKRRLEELERRRKEEEERRRAEEEKR 458
ZC1_h       EQQKEQRRRLEEQQRREREARRQQEREQRRREQEEKRRLEELERRRKEEEERRRAEEEKR 459
ZC2_h       EEQKEQRRRLEEQQRREKELRKQQEREQRRHYEEQMRR-----------------EEERR 404
ZC3_h       EEQKFERRRVEEQQRREREQRKLQEKEQQRRLEDMQAL---------------RREEERR 409
```

Fig. 3B

```
ZC504.4_ce  PAPQQSRKMSEPLLITHVKPEDLDVLASELSKMGG------------------------- 508
NIK_m       RVEREQEYIRRQLEEEQRHLETLQQQLLQEQAMLL------------------------- 493
ZC1_h       RVEREQEYIRRQLEEEQRHLEVLQQQLLQEQAMLLECRWREMEEHRQAERLQRQLQQEQA 519
ZC2_h       RAEHEQEYKRKQLEEQ-----------------------------RQAERLQRQLKQERD 435
ZC3_h       QAEREQEYIRHRLEEEQRQLEILQQQLLQEQALLLEYKRKQLEEQRQSERLQRQLQQEHA 469

ZC504.4_ce  ------HHNGRSREES-MSPPPPAPPPREASISSITDTIDVGELDNGAQAEWDDLKDIMM 561
NIK_m       ------HDHRRPHAQ-QQPPPPQQQDRSKPSFHAPEPKPHYDPADRAREVQWSHLASLKN 548
ZC1_h       YLLSLQHDHRRPHPQHSQQPPPPQQERSKPSFHAPEPKAHYEPADRAREVEDRFRKTNHS 579
ZC2_h       YLVSLQHQR-----------QEQRPVEKKPLYHYKEGMSPSEKPAWAKEVEERSRLNRQS 484
ZC3_h       YLKSLQQQQQQQLQK-QQQQQLLPGDRKPLYHYGRGMNPADKPAWAREVEERTRMNKQQ 528

ZC504.4_ce  NGEGTLRG----------------PNKPLPPTPTDGENTLVSDVRRNGNG---------- 595
NIK_m       NYSPVSRSHSFSDPSPKFAHHHLRSQDPCPPSRSEGLSQSSDSKSEVPEPTQK------- 599
ZC1_h       SPEAQSKQ-------------TGRVLEPPVPSRSESFSNGNSESVHPALQRPAE------ 620
ZC2_h       SPAMPHKV-------------ANRLSDPNLPPRSESFSISGVQPARTPPMLRPVDPQIPH 531
ZC3_h       NSPLAKSK-------------PGS-TGPEPPIPQASPGPPGPLSQTPPMQRPVEPQEGPH 574

ZC504.4_ce  ------------------------------------------------------------ 595
NIK_m       ------------------------------------------------------------ 599
ZC1_h       ------------------------------------------------------------ 620
ZC2_h       LVAVKSQGPALTASQSV------HEQPTKGLSGFQEALNVT----------SHRVEMPRQ 575
ZC3_h       KSLVAHRVPLKPYAAPVPRSQSLQDQPTRNLAAFPASHDPDPAIPAPTATPSARGAVIRQ 634
```

Fig. 3C

```
ZC504.4_ce  -------------------------------NSGHGAYKGKKIPEIRPGIISL-DDDDSD 623
NIK_m       --------------------AWSRSDSDEVPPRVPVRTTSRSPVLSRRDSPLQGGGQQNS 639
ZC1_h       -------------------------------PQVPVRTTSRSPVLSRRDSPLQ-GSGQQN 648
ZC2_h       NSDPTSENPPLPTRIEKFDRSSWLRQEEDIPPKVPQRTTSISPALARKNSPGNGSALGPR 635
ZC3_h       NSDPTSEGPGPSPNPP----AWVRPD-NEAPPKVPQRTSSIATALNTSGAGGSRPAQAVR 689

ZC504.4_ce  SDNE------------------------------EGNEPLMFKPIVRCPFSIFFWFLS-- 651
NIK_m       QAGQ------------------------------RNSTSSIEPRLLWERVEKLVPRPG-- 667
ZC1_h       SQAG------------------------------QRNSTSIEPRLLWERVEKLVPRPG-- 676
ZC2_h       LGSQ------------------------------PIRASNPDLRRTEPILESPLQRTSSG 665
ZC3_h       ARPRSNSAWQIYLQRRAERGTPKPPGPPAQPPGPPNASSNPDLRRSDPG-----WERS-- 742

ZC504.4_ce  --ANVIHSVDGSIPLVKHLIWFQNASSSRGALPDLLPKSPCLRRQINDQTRQMSDDRADE 709
NIK_m       --SGSSSGSSNSGSQPGSNPGSQSGSGERFRVRSSSKSEGSPSPRQESAAKKPDDKKEVF 725
ZC1_h       --SGSSSGSSNSGSQPGSHPGSQSGSGERFRVRSSSKSEGSPSQRLENAVKKPEDKKEVF 734
ZC2_h       SSSSSSTPSSQPSSQGGSQPGSQAGSSERTRVRANSKSEGSPVLPHEPAKVKPEESRDIT 725
ZC3_h       --DSVLPASHGHLP--------QAGSLERNRVGVSSKPDSSPVLSPGNKAKPDDHRSRPG 792

ZC504.4_ce  QPNGFQ--------NSDSR---SSIQHSFSNRDREKSFVGYFGGGAGAGGGTVNRPG--- 755
NIK_m       RSLKPAGEV-----DLTAL---AKELRAVEDVRPPHKVTDYSSSSEESGTTDEEEEDVED 777
ZC1_h       RPLKPA--------DLTAL---AKELRAVEDVRPPHKVTDYSSSSEESGTTDEEDDDVEQ 783
ZC2_h       RPSRPASYKKAIDEDLTALAKELRELRIEETNRPMKKVTDYSSSSEESESSEEEEEDGES 785
ZC3_h       RPADFV------------L---LKERTLDEAPRPPKKAMDYSSSSEEVESSEDDEEEGEG 837
```

Fig. 3D

```
ZC504.4_ce  ------------------------------------------------------------ 755
NIK_m       EGADDSTSGPEDTRAASSPNLSNGETESVKTMIVHDDVESEPAMTP---SKEGTLIV--- 831
ZC1_h       EGADESTSGPEDTRAASSLNLSNGETESVKTMIVHDDVESEPAMTP---SKEGTLIV--- 837
ZC2_h       ETHDGTVAVSDIPRLIPTGAPGSNEQYNVGMVGTHGLETSHADSFSGSISREGTLMIRET 845
ZC3_h       GPAEGS---------RDTPGGRDGDTDSVSTMVVHDVEEITGTQPP---YGGGTMVVQRT 885

ZC504.4_ce  ------------------------------------------------------------ 755
NIK_m       ----------------------------------------------RQTQSASSTLQKHK 845
ZC1_h       ----------------------------------------------RRTQSASSTLQKHK 851
ZC2_h       SGEKKRSGHSDSNGFAGHINLPDLVQQSHSPAGTPTEGLGRVSTHSQEMDSGTEYGMGSS 905
ZC3_h       PEEERNLLHADSNGYT---NLPDVVQPSHSPTENSKGQSPPSKDGSGDYQSRGLVKAPG- 941

ZC504.4_ce  ----------------------------------------RPQDI---NQVQNVTPNSN 772
NIK_m       SSSSFTPFIDPRLLQISPSSGTTVTSVVGFSCDGLRPEAIRQDPT----RKGSVVNVNPT 901
ZC1_h       SSSSFTPFIDPRLLQISPSSGTTVTSVVGFSCDGMRPEAIRQDPT----RKGSVVNVNPT 907
ZC2_h       TKASFTPFVDPRVYQTSPTDEDEEDEESSAAALFTGELLRQEQAKLNEARKISVVNVNPT 965
ZC3_h       -KSSFTMFVDLGIYQPGGSGDSIPITALVGGEGTRLDQLQYDV------RKGSVVNVNPT 994
ZC4_h       -------------------------------------------------------NVNPL 5

ZC504.4_ce  GTPAENDAPEIRKYKKKFSGEILCAALWGVNLLIGTDSGLMLLDRSGQGKVYPLISRRRF 832
NIK_m       NTRPQSDTPEIRKYKKRFNSEILCAALWGVNLLVGTESGLMLLDRSGQGKVYPLISRRRF 961
ZC1_h       NTRPQSDTPEIRKYKKRFNSEILCAALWGVNLLVGTESGLMLLDRSGQGKVYPLINRRRF 967
ZC2_h       NIRPHSDTPEIRKYKKRFNSEILCAALWGVNLLVGTENGLMLLDRSGQGKYYNLINRRRF 1025
ZC3_h       NTRAHSETPEIRKYKKRFNSEILCAALWGVNLLVGTENGLMLLDRSGQGKVYGLIGRRRF 1054
ZC4_h       YVSPACKKPLIHMYEKEFTSEICCGSLWGVNLLLGTRSNLYLMDRSGKADITKLIRRRPF 65
```

Fig. 3E

```
ZC504.4_ce  DQMTVLEGQNILATISGRKRRIRVYYLSWLRQKILRTEGAGSANTTEKRNGWVNVGD---  889
NIK_m       QQMDVLEGLNVLVTISGKKDKLRVYYLSWLRNKILHNDPEV-----EKKQGWTTVGD---  1013
ZC1_h       QQMDVLEGLNVLVTISGKKDKLRVYYLSWLRNKILHNDPEV-----EKKQGWTTVGD---  1019
ZC2_h       QQMDVLEGLNVLVTISGKKNKLRVYYLSWLRNRILHNDPEV-----EKKQGWITVGD---  1077
ZC3_h       QQMDVLEGLNLLITISGKRNKLRVYYLSWLRNKILHNDPEV-----EKKQGWTTVGD---  1106
ZC4_h       RQLQVLEPLNLLITISGHKNRLRVYHLTWLRNKILNNDPES-----KRRQEEMLKTEEAC  120

ZC504.4_ce  -----LQGAIHFKIVRYERIKFLVVGLESSIEIYAWAPKPYHKFMSFKSFGSLSHVPLIV  944
NIK_m       -----LEGCVHYKVVKYERIKFLVIALKSSVEVYAWAPKPYHKFMAFKSFGELLHKPLLV  1068
ZC1_h       -----LEGCVHYKVVKYERIKFLVIALKSSVEVYAWAPKPYHKFMAFKSFGELVHKPLLV  1074
ZC2_h       -----LEGCIHYKVVKYERIKFLVIALKNAVEIYAWAPKPYHKFMAFKSFADLQHKPLLV  1132
ZC3_h       -----MEGCGHYRVVKYERIKFLVIALKSSVEVYAWAPKPYHKFMAFKSFADLPHRPLLV  1161
ZC4_h       KAIDKLTGCEHFSVLQHEETTYIAIALKSSIHLYAWAPKSFDESTAIKVFPTLDHKPVTV  180

ZC504.4_ce  DLTVEDNARLKVLYGSTGGFHAIDLDSAAVYDIYTPAQSGQTTIPHCIVVLPNSNGMQLL  1004
NIK_m       DLTVEEGQRLKVIYGSCAGFHAVDVDSGSVYDIYLPTHIQCSIKPHAIIILPNTDGMELL  1128
ZC1_h       DLTVEEGQRLKVIYGSCAGFHAVDVDSGSVYDIYLPTHIQCSIKPHAIIILPNTDGMELL  1134
ZC2_h       DLTVEEGQRLKVIFGSHTGFHVIDVDSGNSYDIYTPSHIQGNITPHAIVILPKTDGMEML  1192
ZC3_h       DLTVEEGQRLKVIYGSSAGFHAVDVDSGNSYDIYIPVHIQSQITPHAIIFLPNTDGMEML  1221
ZC4_h       DLAIGSEKRLKIFFSSADGYHLIDAESEVMSDVTLPKNPLEIIIPQNIIILPDCLGIGMM  240
```

Fig. 3F

```
ZC504.4_ce  LCYDNEGVYVNTYGRMTKNVVLQWGEMPSSVAYISTGQIMGWGNKAIEIRSVDTGHLDGV  1064
NIK_m       VCYEDEGVYVNTYGRITKDVVLQWGEMPTSVAYIRSNQTMGWGEKAIEIRSVETGHLDGV  1188
ZC1_h       VCYEDEGVYVNTYGRITKDVVLQWGEMPTSVAYIRSNQTMGWGEKAIEIRSVETGHLDGV  1194
ZC2_h       VCYEDEGVYVNTYGRITKDVVLQWGEMPTSVAYIHSNQIMGWGEKAIEIRSVETGHLDGY  1252
ZC3_h       LCYEDEGVYVNTYGRIIKDVVLQWGEMPTSVAYICSNQIMGWGEKAIEIRSVETGHLDGV  1281
ZC4_h       LTFNAEALSVEANEQLFKKILEMWKDIPSSIAFECTDRTTGWGQKAIEVRSLQSRVLESE  300

ZC504.4_ce  FMHKKAQKLKFLCERNDKVFFSSAKGGGSCQIYFMTLNKPGLTNW                 1109
NIK_m       FMHKRAQRLKFLCGRNDKVFFSSVRSGGSSQVYFMTLGRTSLLSW                 1233
ZC1_h       FMHKRAQRLKFLCERNDKVFFASVRSGGSSQVYFMTLGRTSLLSW                 1239
ZC2_h       FMHKRAQRLKFLCERNDKVFFASVRSGGSSQVFFMTLNRNSMMNW                 1297
ZC3_h       FMHKRAQRLKFLCERNDKVFFASVRSGGSSQVYFMTLNRNRIMNW                 1326
ZC4_h       LKRRSIKKLRFLCTRGDKLFFTSTLRNHHSRVYFMTLGKLEELQSNYDV             349
```

Fig. 3G

```
            ..*. *. *****.*.**.**.**************.******.*.******.**...**
KHS1_h    5 LRPAADILRRNPQQDYELVQRVGSGTYGDVYKARNVHTGELAAVKIIKLEPGDDFSLIQQ 64
KHS2_h    1 MNPGFDLSRRNPQEDFELIQRIGSGTYGDVYKARNVNTGELAAIKVIKLEPGEDFAVVQQ 60

            ** *.*.*** ********** *.*******.************************ ***
KHS1_h   65 EIFMVKECKHCNIVAYFGSYLSREKLWICMEYCGGGSLQDIYHVTGPLSELQIAYVCRET 124
KHS2_h   61 EIIMMKDCKHPNIVAYFGSYLRRDKLWICMEFCGGGSLQDIYHVTGPLSELQIAYVSRET 120

            **** ***.*****************.* ********.* ********************
KHS1_h  125 LQGLAYLHTKGKMHRDIKGANILLTDHGDVKLADFGVAAKITATIAKRKSFIGTPYWMAP 184
KHS2_h  121 LQGLYYLHSKGKMHRDIKGANILLTDNGHVKLADFGVSAQITATIAKRKSFIGTPYWMAP 180

            ******..********.**********.******************.************ 
KHS1_h  185 EVAAVEKNGGYNQLCDIWAVGITAIELGELQPPMFDLHPMRALFLMSKSNFQPPKLKDKT 244
KHS2_h  181 EVAAVERKGGYNQLCDLWAVGITAIELAELQPPMFDLHPMRALFLMTKSNFQPPKLKDKM 240

            ***..**.***.*************.** * **.*  *.*.**.********** *. * 
KHS1_h  245 KWSSTFHNFVKIALTKNPKKRPTAERLLTHTFVAQPGLSRALAVELLDKVNNPDNHAHYT 304
KHS2_h  241 KWSNSFHHFVKMALTKNPKKRPTAEKLLQHPFVTQH-LTRSLAIELLDKVNNPD-HSTYH 298

            . **** ** . . * *.**.** * *.* *** *  . *.******** ..*.  *
KHS1_h  305 EADDDDFEPHAIIRHTIRSTNRNARAERTASEINFDKLQFEPPLRKETEARDEMGLS--- 361
KHS2_h  299 DFDDDDPEPLVAVPHRIHSTSRNVREEKTRSEITFGQVKFDPPLRKETEPHHELPDSDGF 358
```

Fig. 4A

```
KHS1_h  362 -------------SDPNFMLQWNP------FV---------------------------D 375
KHS2_h  359 LDSSEEIYYTARSNLDLQLEYGQGHQGGYFLGANKSLLKSVEEELHQRGHVAHLEDDEGD 418

KHS1_h  376 GANTGKSTSKRAIPPPLPPKPRISSYPED-NFPDEEKASTIKHCP--DSESRAPQILRRQ 432
KHS2_h  419 DDESKHSTLKAKIPPPLPPKPKSIFIPQEMHSTEDENQGTIKRCPMSGSPAKPSQVPPRP 478

KHS1_h  433 SSPSCGPVAETSSIGNGDGISKL-MSENTEGSA-------QAPQLPRKNDKRDFPKPAIN 484
KHS2_h  479 PPPR---LPPHKPVALGNGMSSFQLMGERDGSLCQQQNEHRGTNLSRK-EKKDVPKPISN 534

KHS1_h  485 GLPPTPKVLMGACFSKVFDGCPLKINCATSWIHPDTKDQYIIFGTEDGIYTLNLNELHEA 544
KHS2_h  535 GLPPTPKVHMGACFSKVFNGCPLKIHCASSWINPDTRDQYLIFGAEEGIYTLNLNELHET 594

KHS1_h  545 TMEQLFPRKCTWLYVINNTLMSLSEGKTFQLYSHNLIALFEHAK-KPGLAAHIQTHRFPD 603
KHS2_h  595 SMEQLFPRRCTWLYVMNNCLLSIS-GKASQLYSHNLPGLFDYARQMQKLPVAIPAHKLPD 653

KHS1_h  604 RILPRKFALTTKIPDTKGCHKCCIVRNPYTGHKYLCGALQSGIVLLQWYEPMQKFMLIKH 663
KHS2_h  654 RILPRKFSVSAKIPETKWCQKCCVVRNPYTGHKYLCGALQTSIVLLEWVEPMQKFMLIKH 713
```

Fig. 4B

```
                ***.* ** .*****.******.***..*.* . ****.***.* **.******  ..
KHS1_h   664  FDFPLPSPLNVFEMLVIPEQEYPMVCVAISKGTESNQVVQFETINLNSASSWFTEIGAGS  723
KHS2_h   714  IDFPIPCPLRMFEMLVVPEQEYPLVCVGVSRGRDFNQVVRFETVNPNSTSSWFTE--SDT  771

               * .  *********.*****  .*******.****.**.***.***.***.********
KHS1_h   724  QQLDSIHVTQLERDTVLVCLDKFVKIVNLQGKLKSSKKLASELSFDFRIESVVCLQDSVL  783
KHS2_h   772  PQTNVTHVTQLERDTILVCLDCCIKIVNLQGRLKSSRKLSSELTFDFQIESIVCLQDSVL  831

              *********.**.*.********  **.*****************.****.**********
KHS1_h   784  AFWKHGMQGKSFKSDEVTQEISDETRVFRLLGSDRVVVLESRPTENPTAHSNLYILAGHE  843
KHS2_h   832  AFWKHGNQGRSFRSNEVTQEISDSTRIFRLLGSDRVVVLESRPTDNPTANSNLYILAGHE  891

              ***
KHS1_h   844  NSY                                                          846
KHS2_h   892  NSY                                                          894
```

Fig. 4C

```
SULU_ce  MAPAVLQKPGVIKDPSIAALFSNKDPEQRYQDLREIGHGSFGAVYFAYDKKNEQTVAIKK  60
SULU1_h  ------MRKGVLKDPEIDDLFYKDDPEELFIGLHEIGHGSFGAVYFATNAHTNEVVAIKK  54
SULU3_m  --MPSTNRAGSLKDPEIAELFFKEDPEKLFTDLREIGHGSFGAVYFARDVRTNEVVAIKK  58

SULU_ce  MNFSGKQAVEKWNDILKEVSFLNTVVHPHIVDYKACFLKDTTCWLVMEYCIGSAADIVDV  120
SULU1_h  MSYSGKQTHEKWQDILKEVKFLRQLKHPNTIEYKGCYLKEHTAWLVMEYCLGSASDLLEV  114
SULU3_m  MSYSGKQSTEKWQDIIKEVKFLQRIKHPNSIEYKGCYLREHTAWLVMEYCLGSASDLLEV  118

SULU_ce  LRKGMREVEIAAICSQTLDALRYLHSLKRIHRDIKAGNILLSDHAIVKLADFGSASLVDP  180
SULU1_h  HKKPLQEVEIAAITHGALHGLAYLHSHALIHRDIKAGNILLTEPGQVKLADFGSASMASP  174
SULU3_m  HKKPLQEVEIAAITHGALQGLAYLHSHTMIHRDIKAGNILLTEPGQVKLADFGSASMASP  178

SULU_ce  AQTFIGTPFFMAPEVILAMDEGHYTDRADIWSLGITCIELAERRPPLFSMNAMSALYHIA  240
SULU1_h  ANSFVGTPYWMAPEVILAMDEGQYDGKVDIWSLGITCIELAERKPPLFNMNAMSALYHIA  234
SULU3_m  ANSFVGTPYWMAPEVILAMDEGQYDGKVDVWSLGITCIELAERKPPLFNMNAMSALYHIA  238
SULU3_h  ------------------------------------IIELAERKPPLFNMNAMSALYHIA  24

SULU_ce  QNDPPTLSPIDTSEQPEWSLEFVQFIDKCLRKPAEERMSAEECFRHPFIQRSRPSDTIQE  300
SULU1_h  QNDSPTLQSN------EWTDSFRRFVDYCLQKIPQERPTSAELLRHDFVRRDRPLRVLID  288
SULU3_m  QNESPTLQSNMN--------------DSCLQKIPQDRPTSEELLKHMFVLRERPETVLID  284
SULU3_h  QNESPTLQSN------EWSDYFRNFVDSCLQKIPQDRPTSEELLKHIFVLRERPETVLID  78

SULU_ce  LIQRTKNMVLELDNFQYKKMRKLMYLDETEGKEGSEGNGASDDLDFHGNEANSIGRAGDS  360
SULU1_h  LIQRTKDAVRELDNLQYRKMKKILF-----------------------------------  313
SULU3_m  LIQRTKDAVRELDNLQYRKMKKLLF-----------------------------------  309
SULU3_h  LIQRTKDAVRELDNLQYRKMKKLLF-----------------------------------  103
```

Fig. 5A

```
SULU_ce  ASSRSASLTSFRSMQSSGGAGLLVSTNTTGAMDNVHGSSGYGNGSSSTTSSARRRPPIPS 420
SULU1_h  -------------------------------------------------QETRNGPLNES 324
SULU3_m  -------------------------------------------------QEAHNGPAVEA 320
SULU3_h  -------------------------------------------------QEAHNGPAVEA 114

SULU_ce  QMLSSTSTSGVGTMPSHGSVGASITAIAVNPTPSPSEPIPTSQPTSKSESS-SILETAHD 479
SULU1_h  QEDEEDSEHGTSLNREMDSLGSNHSIPSMSVSTGSQSSSVNSMQEVMDESSSELVMMHDD 384
SULU3_m  QEEEEEQDHGVGRTGTVNSVGSNQSIPSMSISASSQSSSVNSLPDASDDKS-ELDMMEGD 379
SULU3_h  QEEEEEQDHGVGRTGTVNSVGSNQSIPSMSISASSQSSSVNSLPDVSDDKS-ELDMMEGD 173

SULU_ce  DPLDTSI------------------RAPVKDLHMPHRAVKERIATLQNHKFATLRSQRII 521
SULU1_h  ESTINSSSSVVHKKDHVFTRDEAGHGDPRPEPRPTQSVQSQALHYRNRERFATIKSASLV 444
SULU3_m  HTVMSNSSVIHLKPEEENYQEEGDPRTRASDPQSPPQVSRHKSHYRNREHFATIRTASLV 439
SULU3_h  HTVMSNSSVIHLKPEEENYREEGDPRTRASDPQSPPQVSRHKSHYRNREHFATIRTASLV 233

SULU_ce  NQEQEEYTKENNMYEQMSKYKHLRQAHHKELQQFEERCALDREQLRVKMDRELEQLTTTY 581
SULU1_h  TRQIHEHEQENELREQMSGYKRMRRQHQKQLIALENKLKAEMDEHRLKLQKEVETHANNS 504
SULU3_m  TRQMQEHEQDSELREQMSGYKRMRRQHQKQLMTLENKLKAEMDEHRLRLDKDLETQRNNF 499
SULU3_h  TRQMQEHEQDSELREQMSGYKRMRRQHQKQLMTLENKLKAEMDEHRLRLDKDLETCRNNF 293

SULU_ce  SKEKMRVRCSQNNELDKRKKDIEDGEKKMKKTKNSQNQQQMKLYSAQQLKEYKYNKEAQK 641
SULU1_h  SIELEKLAKKQVAIIEKEAKVAAADEKKFQQQILAQQKKDLTTFLESQKKQYKICKEKIK 564
SULU3_m  AAEMEKLIKKHQAAMEKEAKVMANEEKKFQQHIQAQQKKELNSFLESQKREYKLRKEQLK 559
SULU3_h  AAEMEKLIKKHQAAMEKEAKVMSNEEKKFQQHIQAQQKKELNSFLESQKREYKLRKEQLK 353
```

Fig. 5B

```
SULU_ce  TRLRSLNM-PRSTYENAMKEVKADLNRVKDARENDFDEKLRAELEDEIVRYRRQQLSNLH 700
SULU1_h  EEMNEDHSTPKKEKQERISKHKENLQHTQAEEEAHLLTQQRLYYDKNCRFFKRKIMIKRH 624
SULU3_m  EELNENQSTPKKEKQEWLSKQKENIQHFQAEEEANLLRRQRQYLELECRRFKRRMLLGRH 619
SULU3_h  EELNENQSTPKKEKQEWLSKQKENIQHFQAEEEANLLRRQRQYLELECRRFKRRMLLGRH 413

SULU_ce  QLEEQLDDEDVNVQERQMDTRHGLLSKQHEMTRDLEIQHLNELHAMKKRHLETQHEAESA 760
SULU1_h  EVEQQNIREELNKKRTQKEMEHAMLIRHDESTRELEYRQLHTLQKLRMDLIRLQHQTELE 684
SULU3_m  NLEQDLVREELNKRQTQKDLEHAMLLRQHESMQELEFRHLNTIQKMRCELIRLQHQTELT 679
SULU3_h  NLEQDLVREELNKRQTQKDLEHAMLLRQHESMQELEFRHLNTIQKMRCELIRLQHQTELT 473

SULU_ce  SQNEYTQRQQDELRKKHAMQSRQQPRDLKIQEAQIRKQYRQVVKTQTRQFKLYLTQMVQV 820
SULU1_h  NQLEYNKRRERELHRKHVMGLRQQPKNLKAMEMQIKKQFQDTCKVQTKQYKALKNHQLEV 744
SULU3_m  NQLEYNKRRERELRRKHVMEVRQQPKSLKSKELQIKKQFQDTCKIQTRQYKALRNHLLET 739
SULU3_h  NQLEYNKRRERELRRKHVMEVRQQPKSLKSKELQIKKQFQDTCKIQTRQYKALRNHLLET 533

SULU_ce  VPKDEQKELTSRLKQDQMQKVALLASQYESQIKKMVQDKTVKLESWQEDEQRVLSEKLEK 880
SULU1_h  TPKNEHKTILKTLKDEQTRKLAILAEQYEQSINEMMASQALRLDEAQEAECQALRLQLQQ 804
SULU3_m  TPKNEHKAI                                                    748
SULU3_h  TPKSEHKAVLKRLKEEQTRKLAILAEQYDHSINEMLSTQALRLDEAQEAECQVLKMQLQQ 593

SULU_ce  ELEELIAYQKKTRATLEEQIKKERTALEERIGTRRAMLEQKIIEEREQMGEMRRLKKEQI 940
SULU1_h  EMELLNAYQSKIKMQTEAQHERELQKLEQRVSLRRAHLEQKIEEELAALQKERSERIKNL 864
SULU3_h  ELELLNAYQSKIKMQAEAQHDRELRELEQRVSLRRALLEQKIEEEMLALQNERTERIRSL 653
```

Fig. 5C

```
SULU_ce  RDRHSQERHRLENHFVRTGSTSRSSGGIAPGVGNSSSIQMAM                        982
SULU1_h  LERQEREIETFDMESLRMGFGNLVTLDFPKEDYR                                898
SULU3_h  LERQAREIEAFDSESMRLGFSNMVLSNLSPEAFSHSYPGASGWSHNPTGGPGPHWGHPMG      713

SULU3_h  GPPQAWGHPMQGGPQPWGHPSGPMQGVPRGSSMGVRNSPQALRRTASGGRTEQGMSRSTS      773

SULU3_h  VTSQISNGSHMSYT                                                    787
```

Fig. 5D

```
             *********************************.**************************
LOK_m      1 MAFANFRRILRLSTFEKRKSREYEHVRRDLDPNDVWEIVGELGDGAFGKVYKAKNKETGA  60
GEK2_h     1 MAFANFRRILRLSTFEKRKSREYEHVRRDLDPNEVWEIVGELGDGAFGKVYKAKNKETGA  60

             ***************************************** ******************
LOK_m     61 LAAAKVIETKSEEELEDYIVEIEILATCDHPYIVKLLGAYYYDGKLWIMIEFCPGGAVDA 120
GEK2_h    61 LAAAKVIETKSEEELEDYIVEIEILATCDHPYIVKLLGAYYHDGKLWIMIEFCPGGAVDA 120

             *****************************.******************************
LOK_m    121 IMLELDRGLTEPQIQVVCRQMLEALNFLHGKRIIHRDLKAGNVLMTLEGDIRLADFGVSA 180
GEK2_h   121 IMLELDRGLTEPQIQVVCRQMLEALNFLHSKRIIHRDLKAGNVLMTLEGDIRLADFGVSA 180

             ************************.******.****************************
LOK_m    181 KNLKTLQKRDSFIGTPYWMAPEVVLCETMKDAPYDYKADIWSLGITLIEMAQIEPPHHEL 240
GEK2_h   181 KNLKTLQKRDSFIGTPYWMAPEVVMCETMKDTPYDYKADIWSLGITLIEMAQIEPPHHEL 240

             *************************************************.***** .***
LOK_m    241 NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLQHPFVSRVTSN 300
GEK2_h   241 NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLEHPFVSSITSN 300

             **********************..********* . * ****.*. *. ***...* *..
LOK_m    301 KALRELVAEAKAEVMEEIEDGREDGEEEDAVDAVPPLVNHTQDSANVTQPSLDSNKLLQD 360
GEK2_h   301 KALRELVAEAKAEVMEEIEDGRDEGEEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEE 360
```

Fig. 6A

```
              * ****.***.*..** ********* .******.   . *.* * ***********.****
LOK_m   361  S-STPLPPSQPQEPVNGPCSQPSGDGPLQTTSPADGLSKNDNDLKVPVPLRKSRPLSMDA  419
GEK2_h  361  SPSTPLAPSQSQDSVNEPCSQPSGDRSLQTTSPPVVAPGNENGLAVPVPLRKSRPVSMDA  420

              ***. .***...*  . ****..****.*************** *.**.** *.  .*.
LOK_m   420  RIQMDEEKQIPDQDENPSPAASKSQKANQSRPNSSALETLGGEALTNGGLELPSSVTPSH  479
GEK2_h  421  RIQVAQEKQVAEQGGDLSPAANRSQKASQSRPNSSALETLGGEKLANGSLEPPAQAAPGP  480

              *** ****.* *********.**.******* ****.* .** .*******.********
LOK_m   480  SKRASDCSNLSTSESMDYGTSLSADLSLNKETGSLSLKGSKLHNKTLKRTRRFVVDGVEV  539
GEK2_h  481  SKRDSDCSSLCTSESMDYGTNLSTDLSLNKEMGSLSIKDPKLYKKTLKRTRKFVVDGVEV  540

              ***************************************.****************
LOK_m   540  SITTSKIISEDEKKDEEMRFLRRQELRELRLLQKEEHRNQTQLSSKHELQLEQMHKRFEQ  599
GEK2_h  541  SITTSKIISEDEKKDEEMRFLRRQELRELRLLQKEEHRNQTQLSNKHELQLEQMHKRFEQ  600

              ********.* ********************.***.***.**********..****** *
LOK_m   600  EINAKKKFYDVELENLERQQKQQVEKMEQDHSVRRKEEAKRIRLEQDRDYAKFQEQLKQM  659
GEK2_h  601  EINAKKKFFDTELENLERQQKQQVEKMEQDHAVRRREEARRIRLEQDRDYTRFQEQLKLM  660

              *****.**********************.**** ****************..***.****
LOK_m   660  KKEVKSEVEKLPRQQRKESMKQKMEEHSQKKQRLDRDFVAKQKEDLELAMRKLTTENRRE  719
GEK2_h  661  KKEVKNEVEKLPRQQRKESMKQKMEEHTQKKQLLDRDFVAKQKEDLELAMKRLTTDNRRE  720
```

Fig. 6B

```
               ******.** ******************************************.*******
LOK_m   720 ICDKERDCLSKKQELLRDREAALWEMEEHQLQERHQLVKQQLKDQYFLQRHDLLRKHEKE 779
GEK2_h  721 ICDKERECLMKKQELLRDREAALWEMEEHQLQERHQLVKQQLKDQYFLQRHELLRKHEKE 780

               ***********.********************.* **************.***.******
LOK_m   780 REQMQRYNQRMMEQLKVRQQQEKARLPKIQRSDGETRMAMYKKSLHINGAGSASEQREKI 839
GEK2_h  781 REQMQRYNQRMIEQLKVRQQQEKARLPKIQRSEGKTRMAMYKKSLHINGGGSAAEQREKI 840

               ************.**********.*****.****************** ***********
LOK_m   840 KQFSQQEEKRQKAERLQQQQKHEHQMRDMVAQCESNMSELQQLQNEKCYLLVEHETQKLK 899
GEK2_h  841 KQFSQQEEKRQKSERLQQQQKHENQMRDMLAQCESNMSELQQLQNEKCHLLVEHETQKLK 900

               ********.***
LOK_m   900 ALDESHNQSLKE                                                 911
GEK2_h  901 ALDESHNQNLKE                                                 912
```

Fig. 6C

```
PAK1_h   MSNNGLDIQDKPPAPPMRNTSTMIGAGSKDAGTLNHGSKPLPPNPEEKKKKDRFYRSIL- 59
PAK65_h  MEETQQKSHLELLSA-------------------NHSLKPLPSVPEEKKPRHKIISIFS- 40
PAK3_m   -MSDSLDNEEKPPAPPLR-----MNSNNRDSSALNHSSKPLPMAPEEKNKKARLRSIFPG 54

PAK1_h   PGDKTNKKKEKERPEISLPSDFEHTIHVGFDAVTGEFTGMPEQWARLLQTSNITKS---- 115
PAK65_h  GTEKGSKKKEKERPEISPPSDFEHTIHVGFDTVTGEFTGMPEQWARLLQTSNITKL---- 96
PAK3_m   GGDKTNKKKEKERPEISLPSDFEHTIHVGFDAVTGEFTGIPEQWARLLQTSNITKL---- 110
PAK4_h   ----MFRKKKKKRPEISAPQNFQHRVHTSFDPKEGKFVGLPPQWQNILDTLRRPKPVVDP 56

PAK1_h   ------------------------------------------------------------ 115
PAK65_h  ------------------------------------------------------------ 96
PAK3_m   ------------------------------------------------------------ 110
PAK4_h   SRITRVQLQPMKTVVRGSAMPVDGYISGLLNDIQKLSVISSNTLRGRSPTSRRRAQSLGL 116

PAK1_h   ------------------------------------------------------------ 115
PAK65_h  ------------------------------------------------------------ 96
PAK3_m   ------------------------------------------------------------ 110
PAK4_h   LGDEHWATDPDMYLQSPQSERTDPHGLYLSCNGGTPAGHKQMPWPEPQSPRVLPNGLAAK 176

PAK1_h   ------------------------------------------------EQKKNPQAVLDV 127
PAK65_h  ------------------------------------------------EQKKNPQAVLDV 108
PAK3_m   ------------------------------------------------EQKKNPQAVLDV 122
PAK4_h   AQSLGPAEFQGASQRCLQLGACLQSSPPGASPPTGTNRHGMKAAKHGSEEARPQSCLVGS 236
```

Fig. 7A

```
PAK1_h  LEFYNSKKTSNSQKYMSFT--DKSAEDYNSSNALNVKAVSETPAVPPVSEDEDDDDDDAT 185
PAK65_h LKFYDS--NTVKQKYLSFT--PPEKDGFPSGTPALNAKGTEAPAVVT----EEEDDDEET 160
PAK3_m  LKFYDSKETVNNQKYMSFTSGDKSAHGYIAAHQSNTKTGSEPPLAPPVSEEEDEEEEEEE 182
PAK4_h  ATGRPGGEGSPSPKTRESSLKRRLFRSMFLSTAATAPPSSSKPGPPPQSKPNSSFRPPQK 296
PAK5_h  ----------------------------------------------ASGAKLAAGRPFNT 14

PAK1_h  ----PPPVIAPRPEHTKSVYTRSVIEPLPVTPTRDVATSPISPTENNTTPPDALTLNTEK 241
PAK65_h ----APPVIAPRPDHTKSIYTRSVIDPVPAPVGDSHVDGAAKSL--------------DK 202
PAK3_m  DDNEPPPVIAPRPEHTKSIYTRSVVESIASPAAPNKEDIPPSAENANSTTLYR---NTDR 239
PAK4_h  DNPPSLVAKAQSLPSDQPVGTFSPLTTSDTSSPQKSLRTAPATGQLPGRSSPA---GSPR 353
PAK5_h  YPRADTDHPSRGAQGEPHDVAPNGPSAGGLAIPQSSSSSSRPPTRARGAPSPGVLGPHAS 74

PAK1_h  QKKKPKMSDEEILEK-------------------------LRSIVSVGDPKKKYTRFEKI 276
PAK65_h QKKKTKMTDEEIHEK-------------------------LRTIVSIGDPKKKYTRYEKI 237
PAK3_m  QRKKSKMTDEEILEK-------------------------LRSIVSVGDPKKKYTRLEKI 274
PAK4_h  TWHAQISTSNLYLPQDPTVAKGALAGEDTGVVTHEQFKAALRMVVDQGDPRLLLDSYVKI 413
PAK5_h  EPQLAPPACTPAAPAVPGPPGPRSPQREPQRVSHEQFRAALQLVVDPGDPRSYLDNFIKI 134

PAK1_h  GQGASGTVYTAMDVATGQEVAIKQMNLQQQPKKELIINEILVMRENKNPNIVNYLDSYLV 336
PAK65_h GQGASGTVFTATDVALGQEVAIKQINLQKQPKKELIINEILVMKELKNPNIVNFLDSYLV 297
PAK3_m  GQGASGTVYTALDIATGQEVAIKQMNLQQQPKKELIINEILVMRENKNPNIVNYLDSYLV 334
PAK4_h  GEGSTGIVCLAREKHSGRQVAVKMMDLRKQQRRELLFNEVVIMRDYQHFNVVEMYKSYLV 473
PAK5_h  GEGSTGIVCIATVRSSGKLVAVKKMDLRKQQRRELLFNEVVIMRDYQHENVVEMYNSYLV 194
```

Fig. 7B

```
PAK1_h   GDELWVVMEYLAGGSLTDVVTETCMDEGQIAAVCRECLQALESLHSNQVIHRDIKSDNIL 396
PAK65_h  GDELFVVMEYLAGRSLTDVVTETCMDEAQIAAVCRECLQALEFLHANQVIHRDIKSDNVL 357
PAK3_m   GDELWVVMEYLAGGSLTDVVTETCMDVGQIAAVCRECLQALDFLHSNQVIHRDIKSDNIL 394
PAK4_h   GEELWVLMEFLQGGALTDIVSQVRLNEEQIATVCEAVLQALAYLHAQGVIHRDIKSDSIL 533
PAK5_h   GDELWVVMEFLEGGALTDIVTHTRMNEEQIAAVCLAVLQALSVLHAQGVIHRDIKSDSIL 254

PAK1_h   LGMDGSVKLTDFGFCAQITPEQSKRSTMVGTPYWMAPEVVTRKAYGPKVDIWSLGIMAIE 456
PAK65_h  LGMEGSVKLTDFGFCAQITPEQSKRSTMVGTPYWMAPEVVTRKAYGPKVDIWSLGIMAIE 417
PAK3_m   LGMDGSVKLTDFGFCAQITPEQSKRSTMVGTPYWMAPEVVTRKAYGPKVDIWSLGIMAIE 454
PAK4_h   LTLDGRVKLSDFGFCAQISKDVPKRKSLVGTPYWMAPEVISRSLYATEVDIWSLGIMVIE 593
PAK5_h   LTHDGRVKLSDFGFCAQVSKEVPRRKSLVGTPYWMAPELISRLPYGPEVDIWSLGIMVIE 314

PAK1_h   MIEGEPPYLNENPLRALYLIATNGTPELQNPEKLSAIFRDFLNRCLEMDVEKRGSAKELL 516
PAK65_h  MVEGEPPYLNENPLRALYLIATNGTPELQNPEKLSPIFRDFLNRCLEMDVEKRGSAKELL 477
PAK3_m   MVEGEPPYLNENPLRALYLIATNGTPELQNPERLSAVFHDFLNRCLEMDVDRRGSAKELL 514
PAK4_h   MVDGEPPYFSDSPVQAMKRLRDSPPPKLKNSHKVSPVLRDFLERMLVRDPQERATAQELL 653
PAK5_h   MVDGEPPYFNEPPLKAMKMIRDNLPPRLKNLHKVSPSLKGFLDRLLVRDPAQRATAAELL 374

PAK1_h   QHQFLKIAKPLSSLTPLIAAAKEATKNNH                                545
PAK65_h  QHPFLKLAKPLSSLTPLIMAAKEAMKSNR                                506
PAK3_m   QHPFLKLAKPLSSLTPLIIAAKEAIKNSSR                               544
PAK4_h   DHPFLLQTGLPECLVPLIQLYRKQTSTC                                 681
PAK5_h   KHPFLAKAGPPASIVPLMRQNRTR                                     398
```

Fig. 7C

SEQ ID NO: 5 STLK2 human Nterm=1-21 kin=22-274
Cterm=275-416
MAHSPVAVQVPGMQNNIADPEELFTKLERIGKGSFGEVFKGIDNRTQQVVAIKIIDLEEA
EDEIEDIQQEITVLSQCDSSYVTKYYGSYLKGSKLWIIMEYLGGGSALDLLRAGPFDEFQ
IATMLKEILKGLDYLHSEKKIHRDIKAANVLLSEQGDVKLADFGVAGQLTDTQIKRNTFV
GTPFWMAPEVIQQSAYDSKADIWSLGITAIELAKGEPPNSDMHPMRVLFLIPKNNPPTLV
GDFTKSFKEFIDACLNKDPSFRPTAKELLKHKFIVKNSKKTSYLTELIDRFKRWKAEGHS
DDESDSEGSDSESTSRENNTHPEWSFTTVRKKPDPKKVQNGAEQDLVQTLSCLSMIITPA
FAELKQQDENNASRNQAIEELEKSIAVAEAACPGITDKMVKKLIEKFQKCSADESP

SEQ ID NO: 6 STLK3 human Nterm=1-31 kin=32-308 Cterm=309-489
(insert=327-352) tail=490-516
TAAPAPAAPAAPAPAPAPAPAAQAVGWPICRDAYELQEVIGSGATAVVQAALCKPRQERV
AIKRINLEKCQTSMDELLKEIQAMSQCSHPNVVTYYTSFVVKDELWLVMKLLSGGSMLDI
IKYIVNRGEHKNGVLEEAIIATILKEVLEGLDYLHRNGQIHRDLKAGNILLGEDGSVQIA
DFGVSAFLATGGDVTRNKVRKTFVGTPCWMAPEVMEQVRGYDFKADMWSFGITAIELATG
AAPYHKYPPMKVLMLTLQNDPPTLETGVEDKEMMKKYGKSFRKLLSLCLQKDPSKRPTAA
ELLKCKFFQKAKNREYLIEKLLTRTPDIAQRAKKVRRVPGSSGHLHKTEDGDWEWSDDEM
DEKSEEGKAAFSQEKSRRVKEENPEIAVSASTIPEQIQSLSVHDSQGPPNANEDYREASS
CAVNLVLRLRNSRKELNDIRFEFTPGRDTADGVSQELFSAGLVDGHDVVIVAANLQKIVD
DPKALKTLTFKLASGCDGSEIPDEVKLIGFAQLSVS

SEQ ID NO: 7 STLK4 human Nterm=absent, kin=1-178, Ctail=179-414,
insert1=198-222, insert2=253-293
KSGVLDXSTIATILREVLEGLEYLHKXGQIHRDVKAGNILXGEDGSVQIADFGVSAFLAT
GGDITRNKVRKTFVGTPCWMAPEVMEQVRGYDFKADIWSFGITAIELATGAAPYHKYPPM
KVLMLTLQNDPPSLETGVQDKEMLKKYGKSFRKMISLCLQKDPEKRPTAAELLRHKFFQK
AKNKEFLQEKTLQRAPTISERAKKVRRVPGSSGRLHKTEDGGWEWSDDEFDEESEEGKAA
ISQLRSPRVKESISNSELFPTTDPVGTLLQVPEQISAHLPQPAGQIATQPTQVSLPPTAE
PAKTAQALSSGSGSQETKIPISLVLRLRNSKKELNDIRFEFTPGRDTAEGVSQELISAGL
VDGRDLVIVAANLQKIVEEPQSNRSVTFKLASGVEGSDIPDDGKLIGFAQLSIS

SEQ ID NO: 8 STLK5 human Nterm=absent, kin=1-222(lacks N-term),
Ctail=224-274
LICTHFMDGMNELAIAYILQGVLKALDYIHHMGYVHRSVKASHILISVDGKVYLSGLRSN
LSMISHGQRQRVVHDFPKYSVKVLPWLSPEVLQQNLQGYDAKSDIYSVGITACELANGHV
PFKDMPATQMLLEKLNGTVPCLLDTSTIPAEELTMSPSRSVANSGLSDSLTTSTPRPSNG
DSPSHPYHRTFSPHFHHFVEQCLQRNPDARPSASTLLNHSFFKQIKRRASEALPELLRPV

Fig. 8A

TPITNFEGSQSQDHSGIFGLVTNLEELEVDDWEF

SEQ ID NO: 13 ZC1 human 1/5/98 Nterm=1-22 kin=23-289
coiled-coil=290-526 pro=527-640 B=641-896 Rab/Rac-BD=897-1239
MANDSPAKSLVDIDLSSLRDPAGIFELVEVVGNGTYGQVYKGRHVKTGQLAAIKVMDVTE
DEEEEIKLEINMLKKYSHHRNIATYYGAFIKKSPPGHDDQLWLVMEFCGAGSITDLVKNT
KGNTLKEDWIAYISREILRGLAHLHIHHVIHRDIKGQNVLLTENAEVKLVDFGVSAQLDR
TVGRRNTFIGTPYWMAPEVIACDENPDATYDYRSDLWSCGITAIEMAEGAPPLCDMHPMR
ALFLIPRNPPPRLKSKKWSKKFFSFIEGCLVKNYMQRPSTEQLLKHPFIRDQPNERQVRI
QLKDHIDRTRKKRGEKDETEYEYSGSEEEEEEVPEQEGEPSSIVNVPGESTLRRDFLRLQ
QENKERSEALRRQQLLQEQQLREQEEYKRQLLAERQKRIEQQKEQRRRLEEQQRREREAR
RQQEREQRRREQEEKRRLEELERRRKEEEERRRAEEEKRRVEREQEYIRRQLEEEQRHLE
VLQQQLLQEQAMLLECRWREMEEHRQAERLQRQLQQEQAYLLSLQHDHRRPHPQHSQQPP
PPQQERSKPSFHAPEPKAHYEPADRAREVEDRFRKTNHSSPEAQSKQTGRVLEPPVPSRS
ESFSNGNSESVHPALQRPAEPQVPVRTTSRSPVLSRRDSPLQGSGQQNSQAGQRNSTSIE
PRLLWERVEKLVPRPGSGSSSGSSNSGSQPGSHPGSQSGSGERFRVRSSSKSEGSPSQRL
ENAVKKPEDKKEVFRPLKPADLTALAKELRAVEDVRPPHKVTDYSSSSEESGTTDEEDDD
VEQEGADESTSGPEDTRAASSLNLSNGETESVKTMIVHDDVESEPAMTPSKEGTLIVRRT
QSASSTLQKHKSSSSFTPFIDPRLLQISPSSGTTVTSVVGFSCDGMRPEAIRQDPTRKGS
VVNVNPTNTRPQSDTPEIRKYKKRFNSEILCAALWGVNLLVGTESGLMLLDRSGQGKVYP
LINRRRFQQMDVLEGLNVLVTISGKKDKLRVYYLSWLRNKILHNDPEVEKKQGWTTVGDL
EGCVHYKVVKYERIKFLVIALKSSVEVYAWAPKPYHKFMAFKSFGELVHKPLLVDLTVEE
GQRLKVIYGSCAGFHAVDVDSGSVYDIYLPTHIQCSIKPHAIIILPNTDGMELLVCYEDE
GVYVNTYGRITKDVVLQWGEMPTSVAYIRSNQTMGWGEKAIEIRSVETGHLDGVFMHKRA
QRLKFLCERNDKVFFASVRSGGSSQVYFMTLGRTSLLSW

SEQ ID NO: 14 ZC2 human Nterm=missing kin=1-255 coiled-coil=256-442
pro=443-626 B=627-954 Rab/RacBD=955-1297
AFGEVYEGRHVKTGQLAAIKVMDVTGDEEEEIKQEINMLKKYSHHRNIATYYGAFIKKNP
PGMDDQLWLVMEFCGAGSVTDLIKNTKGNTLKEEWIAYICREILRGLSHLHQHKVIHRDI
KGQNVLLTENAEVKLVDFGVSAQLDRTVGRRNTFIGTPYWMAPEVIACDENPDATYDFKS
DLWSLGITAIEMAEGAPPLCDMHPMRALFLIPRNPAPRLKSKKWSKKFQSFIESCLVKNH
SQRPATEQLMKHPFIRDQPNERQVRIQLKDHIDRTKKKRGEKDETEYEYSGSEEEEEEND
SGEPSSILNLPRESTLRRDFLRLQLANKERSEALRRQQLEQQQRENEEHKRQLLAERQKR
IEEQKEQRRRLEEQQRREKELRKQQEREQRRHYEEQMRREEERRRAEHEQEYKRKQLEEQ
RQAERLQRQLKQERDYLVSLQHQRQEQRPVEKKPLYHYKEGMSPSEKPAWAKEVEERSRL
NRQSSPAMPHKVANRISDPNLPPRSESFSISGVQPARTPPMLRPVDPQIPHLVAVKSQGP
ALTASQSVHEQPTKGLSGFQEALNVTSHRVEMPRQNSDPTSENPPLPTRIEKFDRSSWLR

Fig. 8B

QEEDIPPKVPQRTTSISPALARKNSPGNGSALGPRLGSQPIRASNPDLRRTEPILESPLQ
RTSSGSSSSSSTPSSQPSSQGGSQPGSQAGSSERTRVRANSKSEGSPVLPHEPAKVKPEE
SRDITRPSRPASYKKAIDEDLTALAKELRELRIEETNRPMKKVTDYSSSSEESESSEEEE
EDGESETHDGTVAVSDIPRLIPTGAPGSNEQYNVGMVGTHGLETSHADSFSGSISREGTL
MIRETSGEKKRSGHSDSNGFAGHINLPDLVQQSHSPAGTPTEGLGRVSTHSQEMDSGTEY
GMGSSTKASFTPFVDPRVYQTSPTDEDEEDEESSAAALFTGELLRQEQAKLNEARKISVV
NVNPTNIRPHSDTPEIRKYKKRFNSEILCAALWGVNLLVGTENGLMLLDRSGQGKVYNLI
NRRRFQQMDVLEGLNVLVTISGKKNKLRVYYLSWLRNRILHNDPEVEKKQGWITVGDLEG
CIHYKVVKYERIKFLVIALKNAVEIYAWAPKPYHKFMAFKSFADLQHKPLLVDLTVEEGQ
RLKVIFGSHTGFHVIDVDSGNSYDIYTPSHIQGNITPHAIVILPKTDGMEMLVCYEDEGV
YVNTYGRITKDVVLQWGEMPTSVAYIHSNQIMGWGEKAIEIRSVETGHLDGVFMHKRAQR
LKFLCERNDKVFFASVRSGGSSQVFFMTLNRNSMMNW

SEQ ID NO: 15 ZC3 human kin=1-255 coiled-coil=256-476 pro=477-680
B=681-983 Rab/RacBD =984-1326
AFGEVYEGRHVKTGQLAAIKVMDVTEDEEEEIKQEINMLKKYSHHRNIATYYGAFIKKSP
PGNDDQLWLVMEFCGAGSVTDLVKNTKGNALKEDCIAYICREILRGLAHLHAHKVIHRDI
KGQNVLLTENAEVKLVDFGVSAQLDRTVGRRNTFIGTPYWMAPEVIACDENPDATYDYRS
DIWSLGITAIEMAEGAPPLCDMHPMRALFLIPRNPPPRLKSKKWSKKFIDFIDTCLIKTY
LSRPPTEQLLKFPFIRDQPTERQVRIQLKDHIDRSRKKRGEKEETEYEYSGSEEEDDSHG
EEGEPSSIMNVPGESTLRREFLRLQQENKSNSEALKQQQQLQQQQRDPEAHIKHLLHQR
QRRIEEQKEERRRVEEQQRREREQRKLQEKEQQRRLEDMQALRREEERRQAEREQEYIRH
RLEEEQRQLEILQQQLLQEQALLLEYKRKQLEEQRQSERLQRQLQQEHAYLKSLQQQQQQ
QQLQKQQQQQLLPGDRKPLYHYGRGMNPADKPAWAREVEERTRMNKQQNSPLAKSKPGST
GPEPPIPQASPGPPGPLSQTPPMQRPVEPQEGPHKSLVAHRVPLKPYAAPVPRSQSLQDQ
PTRNLAAFPASHDPDPAIPAPTATPSARGAVIRQNSDPTSEGPGPSPNPPAWVRPDNEAP
PKVPQRTSSIATALNTSGAGGSRPAQAVRARPRSNSAWQIYLQRRAERGTPKPPGPPAQP
PGPPNASSNPDLRRSDPGWERSDSVLPASHGHLPQAGSLERNRVGVSSKPDSSPVLSPGN
KAKPDDHRSRPGRPADFVLLKERTLDEAPRPPKKAMDYSSSSEEVESSEDDEEEGEGGPA
EGSRDTPGGRDGDTDSVSTMVVHDVEEITGTQPPYGGGTMVVQRTPEEERNLLHADSNGY
TNLPDVVQPSHSPTENSKGQSPPSKDGSGDYQSRGLVKAPGKSSFTMFVDLGIYQPGGSG
DSIPITALVGGEGTRLDQLQYDVRKGSVVNVNPTNTRAHSETPEIRKYKKRFNSEILCAA
LWGVNLLVGTENGLMLLDRSGQGKVYGLIGRRRFQQMDVLEGLNLLITISGKRNKLRVYY
LSWLRNKILHNDPEVEKKQGWTTVGDMEGCGHYRVVKYERIKFLVIALKSSVEVYAWAPK
PYHKFMAFKSFADLPHRPLLVDLTVEEGQRLKVIYGSSAGFHAVDVDSGNSYDIYIPVHI
QSQITPHAIIFLPNTDGMEMLLCYEDEGVYVNTYGRIIKDVVLQWGEMPTSVAYICSNQI
MGWGEKAIEIRSVETGHLDGVFMHKRAQRLKFLCERNDKVFFASVRSGGSSQVYFMTLNR
NRIMNW

Fig. 8C

SEQ ID NO: 16 ZC4 human Nterm kin coiled-coil pro B=missing Rab/RacBD=1-349

NVNPLYVSPACKKPLIHMYEKEFTSEICCGSLWGVNLLLGTRSNLYLMDRSGKADITKLI
RRRPFRQIQVLEPLNLLITISGHKNRLRVYHLTWLRNKILNNDPESKRRQEEMLKTEEAC
KAIDKLTGCEHFSVLQHEETTYIAIALKSSIHLYAWAPKSFDESTAIKVFPTLDHKPVTV
DLAIGSEKRLKIFFSSADGYHLIDAESEVMSDVTLPKNPLEIIIPQNIIILPDCLGIGMM
LTFNAEALSVEANEQLFKKILEMWKDIPSSIAFECTQRTTGWGQKAIEVRSLQSRVLESE
LKRRSIKKLRFLCTRGDKLFFTSTLRNHHSRVYFMTLGKLEELQSNYDV

SEQ ID NO: 18 KHS2 human Nterm=1-13 kin=14-273 A=274-346 Pro=347-534 RabBD =535-894

MNPGFDLSRRNPQEDFELIQRIGSGTYGDVYKARNVNTGELAAIKVIKLEPGEDFAVVQQ
EIIMMKDCKHPNIVAYFGSYLRRDKLWICMEFCGGGSLQDIYHVTGPLSELQIAYVSRET
LQGLYYLHSKGKMHRDIKGANILLTDNGHVKLADFGVSAQITATIAKRKSFIGTPYWMAP
EVAAVERKGGYNQLCDLWAVGITAIELAELQPPMFDLHPMRALFLMTKSNFQPPKLKDKM
KWSNSFHHFVKMALTKNPKKRPTAEKLLQHPFVTQHLTRSLAIELLDKVNNPDHSTYHDF
DDDDPEPLVAVPHRIHSTSRNVREEKTRSEITFGQVKFDPPLRKETEPHHELPDSDGFLD
SSEEIYYTARSNLDLQLEYGQGHQGGYFLGANKSLLKSVEEELHQRGHVAHLEDDEGDDD
ESKHSTLKAKIPPPLPPKPKSIFIPQEMHSTEDENQGTIKRCPMSGSPAKPSQVPPRPPP
PRLPPHKPVALGNGMSSFQLNGERDGSLCQQQNEHRGTNLSRKEKKDVPKPISNGLPPTP
KVHMGACFSKVFNGCPLKIHCASSWINPDTRDQYLIFGAEEGIYTLNLNELHETSMEQLF
PRRCTWLYVMNNCLLSISGKASQLYSHNLPGLFDYARQMQKLPVAIPAHKLPDRILPRKF
SVSAKIPETKWCQKCCVVRNPYTGHKYLCGALQTSIVLLEWVEPMQKFMLIKHIDFPIPC
PLRMFEMLVVPEQEYPLVCVGVSRGRDFNQVVRFETVNPNSTSSWFTESDTPQTNVTHVT
QLERDTILVCLDCCIKIVNLQGRLKSSRKLSSELTFDFQIESIVCLQDSVLAFWKHGMQG
RSFRSNEVTQEISDSTRIFRLLGSDRVVVLESRPTDNPTANSNLYILAGHENSY

SEQ ID NO: 22 SULU1 human N=1-21 kin=22-277 A=278-427 coiled-coil1=428-637 B=638-751 coiled-coil2=752-898

MRKGVLKDPEIDDLFYKDDPEELFIGLHEIGHGSFGAVYFATNAHTNEVVAIKKMSYSGK
QTHEKWQDILKEVKFLRQLKHPNTIEYKGCYLKEHTAWLVMEYCLGSASDLLEVHKKPLQ
EVEIAAITHGALHGLAYLHSHALIHRDIKAGNILLTEPGQVKLADFGSASMASPANSFVG
TPYWMAPEVILAMDEGQYDGKVDIWSLGITCIELAERKPPLFNMNAMSALYHIAQNDSPT
LQSNEWTDSFRRFVDYCLQKIPQERPTSAELLRHDFVRRDRPLRVLIDLIQRTKDAVREL
DNLQYRKMKKILFQETRNGPLNESQEDEEDSEHGTSLNREMDSLGSNHSIPSMSVSTGSQ
SSSVNSMQEVMDESSSELVMMHDDESTINSSSSVVHKKDHVFTRDEAGHGDPRPEPRPTQ
SVQSQALHYRNRERFATIKSASLVTRQIHEHEQENELREQMSGYKRMRRQHQKQLIALEN
KLKAEMDEHRLKLQKEVETHANNSSIELEKLAKKQVAIIEKEAKVAAADEKKFQQQILAQ

Fig. 8D

QKKDLTTFLESQKKQYKICKEKIKEEMNEDHSTPKKEKQERISKHKENLQHTQAEEEAHL
LTQQRLYYDKNCRFFKRKIMIKRHEVEQQNIREELNKKRTQKEMEHAMLIRHDESTRELE
YRQLHTLQKLRMDLIRLQHQTELENQLEYNKRRERELHRKHVMGLRQQPKNLKAMEMQIK
KQFQDTCKVQTKQYKALKNHQLEVTPKNEHKTILKTLKDEQTRKLAILAEQYEQSINEMM
ASQALRLDEAQEAECQALRLQLQQEMELLNAYQSKIKMQTEAQHERELQKLEQRVSLRRA
HLEQKIEEELAALQKERSERIKNLLERQEREIETFDMESLRMGFGNLVTLDFPKEDYR

SEQ ID NO: 23 SULU3 human Nterm=missing kin partial=1-66 A=67-215
coiled-coil1=216-425 B=426-539 coiled-coil2=540-786 Ctail=687-786
IELAERKPPLFNMNAMSALYHIAQNESPTLQSNEWSDYFRNFVDSCLQKIPQDRPTSEEL
LKHIFVLRERPETVLIDLIQRTKDAVRELDNLQYRKMKKLLFQEAHNGPAVEAQEEEEEQ
DHGVGRTGTVNSVGSNQSIPSMSISASSQSSSVNSLPDVSDDKSELDMMEGDHTVMSNSS
VIHLKPEEENYREEGDPRTRASDPQSPPQVSRHKSHYRNREHFATIRTASLVTRQMQEHE
QDSELREQMSGYKRMRRQHQKQLMTLENKLKAEMDEHRLRLDKDLETQRNNFAAEMEKLI
KKHQAAMEKEAKVMSNEEKKFQQHIQAQQKKELNSFLESQKREYKLRKEQLKEELNENQS
TPKKEKQEWLSKQKENIQHFQAEEEANLLRRQRQYLELECRRFKRRMLLGRHNLEQDLVR
EELNKRQTQKDLEHAMLLRQHESMQELEFRHLNTIQKMRCELIRLQHQTELTNQLEYNKR
RERELRRKHVMEVRQQPKSLKSKELQIKKQFQDTCKIQTRQYKALRNHLLETTPKSEHKA
VLKRLKEEQTRKLAILAEQYDHSINEMLSTQALRLDEAQEAECQVLKMQLQQELELLNAY
QSKIKMQAEAQHDRELRELEQRVSLRRALLEQKIEEEMLALQNERTERIRSLLERQAREI
EAFDSESMRLGFSNMVLSNLSPEAFSHSYPGASGWSHNPTGGPGPHWGHPMGGPPQAWGH
PMQGGPQPWGHPSGPMQGVPRGSSMGVRNSPQALRRTASGGRTEQGMSRSTSVTSQISNG
SHMSYT

SEQ ID NO: 24 SULU3 murine Nterm=1-25 kin=26-273 A=274-422
cc1=423-632 B=633-748 cc2=missing
MPSTNRAGSLKDPEIAELFFKEDPEKLFTDLREIGHGSFGAVYFARDVRTNEVVAIKKMS
YSGKQSTEKWQDIIKEVKFLQRIKHPNSIEYKGCYLREHTAWLVMEYCLGSASDLLEVHK
KPLQEVEIAAITHGALQGLAYLHSHTMIHRDIKAGNILLTEPGQVKLADFGSASMASPAN
SFVGTPYWMAPEVILAMDEGQYDGKVDVWSLGITCIELAERKPPLFNMNAMSALYHIAQN
ESPTLQSNMNDSCLQKIPQDRPTSEELLKHMFVLRERPETVLIDLIQRTKDAVRELDNLQ
YRKMKKLLFQEAHNGPAVEAQEEEEEQDHGVGRTGTVNSVGSNQSIPSMSISASSQSSSV
NSLPDASDDKSELDMMEGDHTVMSNSSVIHLKPEEENYQEEGDPRTRASDPQSPPQVSRH
KSHYRNREHFATIRTASLVTRQMQEHEQDSELREQMSGYKRMRRQHQKQLMTLENKLKAE
MDEHRLRLDKDLETQRNNFAAEMEKLIKKHQAAMEKEAKVMANEEKKFQQHIQAQQKKEL
NSFLESQKREYKLRKEQLKEELNENQSTPKKEKQEWLSKQKENIQHFQAEEEANLLRRQR
QYLELECRRFKRRMLLGRHNLEQDLVREELNKRQTQKDLEHAMLLRQHESMQELEFRHLN
TIQKMRCELIRLQHQTELTNQLEYNKRRERELRRKHVMEVRQQPKSLKSKELQIKKQFQD

Fig. 8E

TCKIQTRQYKALRNHLLETTPKNEHKAI

SEQ ID NO: 26 GEK2 human N=1-33 kin=34-294 A=295-337 B=338-472 215 coiled-coil1=473-724 215 coiled-coil2=725-912

MAFANFRRILRLSTFEKRKSREYEHVRRDLDPNEVWEIVGELGDGAFGKVYKAKNKETGA
LAAAKVIETKSEEELEDYIVEIEILATCDHPYIVKLLGAYYHDGKLWIMIEFCPGGAVDA
IMLELDRGLTEPQIQVVCRQMLEALNFLHSKRIIHRDLKAGNVLMTLEGDIRLADFGVSA
KNLKTLQKRDSFIGTPYWMAPEVVMCETMKDTPYDYKADIWSLGITLIEMAQIEPPHHEL
NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLEHPFVSSITSN
KALRELVAEAKAEVMEEIEDGRDEGEEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEE
SPSTPLAPSQSQDSVNEPCSQPSGDRSLQTTSPPVVAPGNENGLAVPVPLRKSRPVSMDA
RIQVAQEKQVAEQGGDLSPAANRSQKASQSRPNSSALETLGGEKLANGSLEPPAQAAPGP
SKRDSDCSSLCTSESMDYGTNLSTDLSLNKEMGSLSIKDPKLYKKTLKRTRKFVVDGVEV
SITTSKIISEDEKKDEEMRFLRRQELRELRLLQKEEHRNQTQLSNKHELQLEQMHKRFEQ
EINAKKKFFDTELENLERQQKQQVEKMEQDHAVRRREEARRIRLEQDRDYTRFQEQLKLM
KKEVKNEVEKLPRQQRKESMKQKMEEHTQKKQLLDRDFVAKQKEDLELAMKRLTTDNRRE
ICDKERECLMKKQELLRDREAALWEMEEHQLQERHQLVKQQLKDQYFLQRHELLRKHEKE
REQMQRYNQRMIEQLKVRQQQEKARLPKIQRSEGKTRMAMYKKSLHINGGGSAAEQREKI
KQFSQQEEKRQKSERLQQQQKHENQMRDMLAQCESNMSELQQLQNEKCHLLVEHETQKLK
ALDESHNQNLKE

SEQ ID NO: 29 PAK4 human Rac=1-51 A=52-224 Nterm=225-393 kin=394-658 Ctail=659-681 residues 13-23 (SAPQNFQHRVH)= Cdc42 /Rac-binding motif

MFRKKKKKRPEISAPQNFQHRVHTSFDPKEGKFVGLPPQWQNILDTLRRPKPVVDPSRIT
RVQLQPMKTVVRGSAMPVDGYISGLLNDIQKLSVISSNTLRGRSPTSRRRAQSLGLLGDE
HWATDPDMYLQSPQSERTDPHGLYLSCNGGTPAGHKQMPWPEPQSPRVLPNGLAAKAQSL
GPAEFQGASQRCLQLGACLQSSPPGASPPTGTNRHGMKAAKHGSEEARPQSCLVGSATGR
PGGEGSPSPKTRESSLKRRLFRSMFLSTAATAPPSSSKPGPPPQSKPNSSFRPPQKDNPP
SLVAKAQSLPSDQPVGTFSPLTTSDTSSPQKSLRTAPATGQLPGRSSPAGSPRTWHAQIS
TSNLYLPQDPTVAKGALAGEDTGVVTHEQFKAALRMVVDQGDPRLLLDSYVKIGEGSTGI
VCLAREKHSGRQVAVKMMDLRKQQRRELLFNEVVIMRDYQHFNVVEMYKSYLVGEELWVL
MEFLQGGALTDIVSQVRLNEEQIATVCEAVLQALAYLHAQGVIHRDIKSDSILLTLDGRV
KLSDFGFCAQISKDVPKRKSLVGTPYWMAPEVISRSLYATEVDIWSLGIMVIEMVDGEPP
YFSDSPVQAMKRLRDSPPPKLKNSHKVSPVLRDFLERMLVRDPQERATAQELLDHPFLLQ
TGLPECLVPLIQLYRKQTSTC

Fig. 8F

SEQ ID NO: 30 PAK5 human Rac A=missing Nterm partial=1-114
kin=115-379 Ctail=380-398
ASGAKLAAGRPFNTYPRADTDHPSRGAQGEPHDVAPNGPSAGGLAIPQSSSSSSRPPTRA
RGAPSPGVLGPHASEPQLAPPACTPAAPAVPGPPGPRSPQREPQRVSHEQFRAALQLVVD
PGDPRSYLDNFIKIGEGSTGIVCIATVRSSGKLVAVKKMDLRKQQRRELLFNEVVIMRDY
QHENVVEMYNSYLVGDELWVVMEFLEGGALTDIVTHTRMNEEQIAAVCLAVLQALSVLHA
QGVIHRDIKSDSILLTHDGRVKLSDFGFCAQVSKEVPRRKSLVGTPYWMAPELISRLPYG
PEVDIWSLGIMVIEMVDGEPPYFNEPPLKAMKMIRDNLPPRLKNLHKVSPSLKGFLDRLL
VRDPAQRATAAELLKHPFLAKAGPPASIVPLMRQNRTR

Fig. 8G

SEQ ID NO: 1 STLK2 HUMAN
TAACAGCCCACCTCCTAGCCCCGGGCTACGCGCCGCCAGCCCAGTAACCCCACTTTTGTG
TGTCCTCCCAGGCCCCGATCGAAAAGCCTGGGAGGGCCGCCGAACTACCCCCGGAGGGAG
GAGCCAGTCCGAACCCAAGGCGCCACCGCCGCAGAAGCGGAGCGAGGCAGCATTCGCCTC
CATGGCCCACTCGCCGGTGGCTGTCCAAGTGCCTGGGATGCAGAATAACATAGCTGATCC
AGAAGAACTGTTCACAAAATTAGAGCGCATTGGGAAAGGCTCATTTGGGGAAGTTTTCAA
AGGAATTGATAACCGTACCCAGCAAGTCGTTGCTATTAAAATCATAGACCTTGAGGAAGC
CGAAGATGAAATAGAAGACATTCAGCAAGAAATAACTGTCTTGAGTCAATGTGACAGCTC
ATATGTAACAAAATACTATGGGTCATATTTAAAGGGGTCTAAATTATGGATAATAATGGA
ATACCTGGGCGGTGGTTCAGCACTGGATCTTCTTCGAGCTGGTCCATTTGATGAGTTCCA
GATTGCTACCATGCTAAAGGAAATTTTAAAAGGTCTGGACTATCTGCATTCAGAAAAGAA
AATTCACCGAGACATAAAAGCTGCCAATGTCTTGCTCTCAGAACAAGGAGATGTTAAACT
TGCTGATTTTGGAGTTGCTGGTCAGCTGACAGATACACAGATTAAAAGAAATACCTTTGT
GGGAACTCCATTTTGGATGGCTCCTGAAGTTATTCAACAGTCAGCTTATGACTCAAAAGC
TGACATTTGGTCATTGGGAATTACTGCTATTGAACTAGCCAAGGGAGAGCCACCTAACTC
CGATATGCATCCAATGAGAGTTCTGTTTCTTATTCCCAAAAACAATCCTCCAACTCTTGT
TGGAGACTTTACTAAGTCTTTTAAGGAGTTTATTGATGCTTGCCTGAACAAAGATCCATC
ATTTCGTCCTACAGCAAAAGAACTTCTGAAACACAAATTCATTGTAAAAAATTCAAAGAA
GACTTCTTATCTGACTGAACTGATAGATCGTTTTAAGAGATGGAAGGCAGAAGGACACAG
TGATGATGAATCTGATTCCGAGGGCTCTGATTCGGAATCTACCAGCAGGGAAAACAATAC
TCATCCTGAATGGAGCTTTACCACCGTACGAAAGAAGCCTGATCCAAAGAAAGTACAGAA
TGGGGCAGAGCAAGATCTTGTGCAAACCCTGAGTTGTTTGTCTATGATAATCACACCTGC
ATTTGCTGAACTTAAACAGCAGGACGAGAATAACGCTAGCAGGAATCAGGCGATTGAAGA
ACTCGAGAAAAGTATTGCTGTGGCTGAAGCCGCCTGTCCCGGCATCACAGATAAAATGGT
GAAGAAACTAATTGAAAAATTTCAAAAGTGTTCAGCAGACGAATCCCCCTAAGAAACTTA
TTATTGGCTTCTGTTTCATATGGACCCAGAGAGCCCCACCAAACCTACGTCAAGATTAAC
AATGCTTAACCCATGAGCTCCATGTGCCTTTTGGATCTTTGCAACACTGAAGATTTGGAA
GAAGCTATTAAACTATTTTGTGATGGCGTTTATCATTTTATATTTTGAAAGGATTATTTT
GTAAGGAATAACTTTTAATACTATAGTTTCACCTGTATTCTAGTAAATGTTGAGACACCG
TTTTGCTTTTAAGTATCCCTATTTCTTAAGTTACGAGGATGAATACCTTTCACATTTTGA
TCTTTAGTTGACTCTACAGTCATGAAACATACAGGTCTTTCAAAGTCATTCTCAATATTC
AGCTTTTGTAAATTATCAAGCTTCAAAAAGCTTTTTTTTAAAAAAAAAAACATGCATATT
CTAAAAATGACTATTGGTGGGGAGGTGTAAATAAGTCATACCTTCTTAAAACAGAAAATT
TAAGTAAAGTCTTTTAAATGAAACCTGTAAAAGTATTGACTCTTCTACCAAGTTGGTATG
ATATTCCAGGCAGCTCAATGATTATCACATTTGAGACCCTGTGTTTGAAGCATTTACAGG
CAATGTACAGCAACAGAGGTACCTCTTGGTGTATAGTATTTACATTCTCTTTTAGGTAGA
AGAGGCAATTTTACCCTTATTTCACATGGTTAGAAATTTAAAGCAAGATCATTTACCCAA

Fig. 9A

GGATAGGTGTTTGGTAATGTTGAAGGAGTTAGTCTGGCTTCATGTTTTACATCTTCAACT
AAAATCCCATACTATCTGCTTGGATTTGGAGAGCCAAAAAATAAAGCTGATTGTCATGTG
ATTAAATATCTGATCAACAGGTATGAATATAACTTAAATCAGCATATTTTTGCCATGGTA
ATAAATTGTCCTATAAACTATTTATATATTTTTGTTCTTCATAATTATCACTAATAAGCA
TCAGTTTGTTGTTTTTAAAAGGATATTTAAGTGAGCATTTTCTAGTTCATATGAAAATAA
CCATAGTACAGGATGATTTCTGTCCACACAAAGGTTAAATTAGATTGCACAGTTAATTTT
CACTTATATTTATGGTACTATTATGTGGGTGATGCCTTTTTCTTTTAAGCCCAGTACATA
TATTATGCCTGCCTAAGTTCTGAACTGGGGCTGTATTTCAGTAGTTGTAGAATTATTGAT
ATTTAGTTTTGATAGCTAATGTTTAATTGTTTGGATCTGCACAGTTTGGTTTTTGCACAA
AAGTCATTTAAAAAAATCTGAGTAATTGTCAAATATTAAAAGAAAGATATTCTTCCTGTA
AGGAATACAGTTTTTAGTCAAAGTGGCCATTACATCCTCTTTTTAATTTACATAATACAG
ATACTTGAGAAAGTTGTTGTGGTGTTGTATGCCAAGAAAATTCTTTTTATTGGTGCCTAT
ATTGTAACAATTATTTTTAATGCATTGTATTTTGAAGTAACGGTTCAGTTAAATTTTTCA
CCTGCTGTGTAACTGAAACACAATTACAGTTTATAATCATCTGTAGAAGTCTGGAGATAA
TTTTGCAACTCATGTTATGGGTTAAATGAATATTTTTGTAAAAGTAAAAGCAACAAATTT
ATAAATTGATTATTTGAAACTTTACAACACAATTGCATCCCAAATACAAATTGTATTGCT
TATTCATTATAGCTATTCGTCCTGTAATCTGTTTCTAGGTGAAGCATACTCCAGTGTTTT
AGGGGTTTTGAAAATAAATATTTAAATTTCACAGTCAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAA

SEQ ID NO: 2 STLK3 HUMAN
GACAGCAGCGCCGGCCCCGGCAGCTCCCGCGGCCCCGGCCCCGGCCCCGGCCCCGGCCCC
GGCGGCACAGGCTGTCGGCTGGCCCATCTGCAGGGACGCGTACGAGCTGCAGGAGGTTAT
CGGCAGTGGAGCTACTGCTGTGGTTCAGGCAGCCCTATGCAAACCCAGGCAAGAACGTGT
AGCAATAAAACGGATCAACTTGGAAAAATGCCAGACCAGTATGGATGAACTATTAAAAGA
AATTCAAGCCATGAGTCAGTGCAGCCATCCCAACGTAGTGACCTATTACACCTCTTTTGT
GGTCAAAGATGAACTTTGGCTGGTCATGAAATTACTAAGTGGAGGTTCAATGTTGGATAT
CATAAAATACATTGTCAACCGAGGAGAACACAAGAATGGAGTTCTGGAAGAGGCAATAAT
AGCAACAATTCTTAAAGAGGTTTTGGAAGGCTTAGACTATCTACACAGAAACGGTCAGAT
TCACAGGGATTTGAAAGCTGGTAATATTCTTCTGGGTGAGGATGGTTCAGTACAAATAGC
AGATTTTGGGGTAAGTGCGTTCCTAGCAACAGGGGGTGATGTTACCCGAAATAAAGTAAG
AAAAACATTCGTTGGCACCCCATGTTGGATGGCTCCTGAAGTCATGGAACAGGTGAGAGG
CTATGACTTCAAGGCTGACATGTGGAGTTTTGGAATAACTGCCATTGAATTAGCAACAGG
AGCAGCGCCTTATCACAAATATCCTCCCATGAAAGTGTTAATGTTGACTTTGCAAAATGA
TCCACCCACTTTGGAAACAGGGGTAGAGGATAAAGAAATGATGAAAAAGTACGGCAAGTC
CTTTAGAAAATTACTTTCACTGTGTCTTCAGAAAGATCCTTCCAAAAGGCCCACAGCAGC
AGAACTTTTAAAATGCAAATTCTTCCAGAAAGCCAAGAACAGAGAGTACCTGATTGAGAA
GCTGCTTACAAGAACACCAGACATAGCCCAAAGAGCCAAAAAGGTAAGAAGAGTTCCTGG

Fig. 9B

GTCAAGTGGTCACCTTCATAAAACCGAAGACGGGGACTGGGAGTGGAGTGACGACGAGAT
GGATGAGAAGAGCGAAGAAGGGAAAGCAGCTTTTTCTCAGGAAAAGTCACGAAGAGTAAA
AGAAGAAAATCCAGAGATTGCAGTGAGTGCCAGCACCATCCCCGAACAAATACAGTCCCT
CTCTGTGCACGACTCTCAGGGCCCACCCAATGCTAATGAAGACTACAGAGAAGCTTCTTC
TTGTGCCGTGAACCTCGTTTTGAGATTAAGAAACTCCAGAAAGGAACTTAATGACATACG
ATTTGAGTTTACTCCAGGAAGAGATACAGCAGATGGTGTATCTCAGGAGCTCTTCTCTGC
TGGCTTGGTGGATGGTCACGATGTAGTTATAGTGGCTGCTAATTTACAGAAGATTGTAGA
TGATCCCAAAGCTTTAAAAACATTGACATTTAAGTTGGCTTCTGGCTGTGATGGGTCGGA
GATTCCTGATGAAGTGAAGCTGATTGGGTTTGCTCAGTTGAGTGTCAGCTGATGTATGTC
CCTTGATGTCACCCTGATCTGTCATGCCCCACCGCCACCCCTACTCCCTTCAACCCTCCC
TCTTTCTGCCCATTTCCTCCCACCCCCTCACTCCCATTTCCTAGCAAAATCAGAAGATTG
TGAAGAGGCCGGCTTCAACAAAATGGGATAAAAAAATAATTTTTTAAAACTTACAACACT
CCGAGTTCTGCTTTATTCTCTAGCAATCCACAGTACAAGAACAAGCAAATGCCACAGCTG
CACGACTGTTGCTCATTTTTCCAAAAGCTATTTAATATTCTTAGCAATCAATTTGGATAT
CCCTTAAGTGAAAAGAATCTGAAATACACTCAGGTGGTCTTATTTATTGGCAACAAAAGG
AATTTTCTATCCAGAAGCCTATTTCTCCTTTCATTGTTGTTATTTCTGTTATAATACTTT
AATTGTACATCTGACAATACTGCCTCTTTTATGTTGTATTTAGAAATTAATATACTTATA
AAATTAAGATTTATTAGCCAAACTTGAATTCTAGTTTTAAAACTGACTGTGAATTTTATT
TTTCATATATTTATGCATTACACACCTTAGCTATAAGAAAAAAAGGGTTTTGATTATATG
CTTCTTGCAGTTAATCTCGTTATTTAAACAAAAAGTTTTGGGTCTATCTTTGGAGTATTT
GTAACTTCTAAATTTTGAAATGACTGAATTAGGAATTTGGATGCTTATTCTTTTAGTCTG
TTTGCCTAAAAACCAATTTACAATCTGACTGTCTCTTGGGAGAGGGAGGTGCCTTGCAAA
CTTTCACATTAAGAATGTGCCTGAGGCTGCTTTACTCTGGAATAGTCTCAGATCTAAAAT
TTCCTCTATATAAGGTGGCATATGTTAAGTTTTGCTTCATTGGACCGTTTAGAATGCTAT
GTAAAATGTTGCCATTCTGTTAGATTGCTAACTATATACCCATCTCTGATTTGGCTCTCC
TTAAGTGATAGGATTTGTTATTCTAAAGGTGATAAACTTGAAAATATCAGAATCTGAGTT
TTACTTGAAATTTTGCAGAATACCCAGGTGGAGTGAAAATTGGAAGGGTTTTGTGCAATG
ACTAAAAGGTAAAACGCTGTTAAGGTTCAAGAATCAATACTTTCAACCCAAGTAGCCCTC
TGCTTGACTGTATATTATGGAACTAGTAAACCTTAGGATTTTGAAAATTGGAGTCTAATC
TTTCAAGGAGGTGGGCTCCCAGGATGGTACCATTGCTCTTTCCTAGCTAACCCTAGATAT
GGCAGCTCTTTAATGTACTTCAAAAAGCAAATATATATTACTAAGGAAAAAAAGTTATTT
ATAATTGCCTTGTCATAATTGTTAAGGTGTTCTAGAGCCATTTGCATACAATTTAATGTA
ATTTCATTCCATTCTATTGTTTACACAACGATTACTCGAAGATGACTGCAAAGGTAAAAG
GAAAATAAAAGTGTATTGCACAATGAAAAA

SEQ ID NO: 3 STLK4 HUMAN
CAAAAGTGGAGTCCTAGATGANTCTACCATTGCTACGATACTCCGAGAAGTACTGGAAGG
GCTGGAATATCTGCATAAAANTGGACAGATCCACAGAGATGTGAAAGCTGGAAACATTCT

Fig. 9C

TNTTGGAGAAGATGGCTCAGTACAGATTTCAGACTTTGGGGTTAGTGCTTTTTTAGCAAC
TGGTGGTGATATTACCCGAAATAAAGTGAGAAAGACCTTTGTTGGCACCCCTTGTTGGAT
GGCACCTGAAGTTATGGAACAGGTCCGTGGTTATGATTTCAAAGCTGATATTTGGAGTTT
TGGAATTACAGCAATTGAATTGGCTACAGGGGCGGCTCCTTATCATAAATATCCACCAAT
GAAGGTTTTAATGCTGACACTGCAGAACGATCCTCCTTCTTTGGAAACTGGTGTTCAAGA
TAAAGAAATGCTGAAAAAATATGGAAAATCATTTAGAAAAATGATTTCATTGTGCCTTCA
AAAAGATCCAGAAAAAAGACCAACAGCAGCAGAACTATTAAGGCACAAATTTTTCCAGAA
AGCAAAGAATAAAGAATTTCTTCAAGAAAAAACATTGCAGAGAGCACCAACCATTTCTGA
AAGAGCAAAAAAGGTTCGGAGAGTACCAGGTTCCAGTGGGCGTCTTCATAAGACAGAGGA
TGGAGGCTGGGAGTGGAGTGATGATGAATTTGATGAAGAAAGTGAGGAAGGGAAAGCAGC
AATTTCACAACTCAGGTCTCCCCGAGTGAAAGAATCAATATCAAATTCTGAGCTCTTTCC
AACAACTGATCCTGTGGGTACTTTGCTCCAAGTTCCAGAACAGATCTCTGCTCATCTACC
TCAGCCAGCTGGGCAGATTGCTACACAGCCAACTCAAGTCTCTCTCCCACCCACCGCAGA
GCCAGCAAAAACAGCTCAGGCTTTGTCTTCAGGATCAGGTTCACAAGAAACCAAGATCCC
AATCAGTCTAGTACTAAGATTAAGGAATTCCAAAAAAGAACTAAATGATATTCGATTTGA
ATTTACTCCTGGGAGAGATACAGCAGAGGGTGTCTCTCAGGAACTCATTTCTGCTGGCCT
GGTCGACGGAAGGGATTTAGTAATAGTGGCAGCTAATTTGCAGAAAATTGTGGAAGAACC
TCAGTCAAATCGATCTGTCACTTTCAAACTGGCATCTGGTGTCGAAGGCTCAGATATTCC
TGATGATGGTAAACTGATAGGATTTGCCCAGCTCAGCATCAGCTAAACCACAACCCTGGA
AGAGGCGGCCTAAGGAGATTCCACACATGCGTATCTCTGTTGCTTCTATTGGCCTAAACC
CACTACTGCCAAAGAACCCAGCAACAAACCTCCCGGCTAGGAGCTTTAGAAGTCTTTATG
TTCTTCCTGCCATCATTCCTCCTTTTCCCACAGGGAAAGAAAAGTTGGATCACTAGTGGC
CAGCATCCCCAGAGTTCCGTTAGTAAACTTACTTCATATGTCCCCTGTCTTCCTCCATCT
GAGAAGTGGCCCATGTGCTTCAAGGCCCAGGAGGGAGATCTGTCAGCTCATTCTTGCCTT
ACTCCAATGATGGCCCAGGTGGAAAAGTAGCAGCTGTATCGGGCTTCCTCATCCTGCCTG
TTCCCCCACACCTGCCAGGATATGGACATCTTGGGATATCTCTTTACCACTGAAGTAGAA
TTGATTGTTCAGCTGGAGCCCAGAGAATTTAATTTAATGTTTTTTCTTTGTACCTGATGT
GAATTCTAGCAACCTTTGTTAGGAAAAAGCACAGCCTCAGATGGAGGCAGCCTAAACTGT
GTTCTTGTTTTGTTCATGGTGTTTCTAAGCGTTTTGCTGAAGCTGCTCTCAGGCACCCCC
TTCTTCATTGCTCTCTCCAGAAAGGGTTGCTAGCCTTAACTTCAGCTGGTGCAAAACATC
TGACTGTAGCCGAACTTCAGCCATCAGATCCTTCAAAGTGGAACTTTGGATTGTTTTTAC
AGACAACATCGAGTAATGGCTTGTAAATGTGAATTTTGCCAGAGGTGGTTTTTGAACAGG
AAAATCATAATTCATATCATTGGAGAAGTATTTATTTTCAAATATCAAATTGAAGAAAAA
CTCAATCCTCCCATGAAAATCAGTTCGCCTGGCCTCCAAGTCGTGAGGAAATGGGTATGC
AAGGCTGAGATTTCTACAGCAATAAAGGAGACACACACTGGGCCAGAGAGGCCTGCCTTC
TGCCTGCTCTCCTGCACTGACCCTTTGGAGGGGGTCTCTGTGTGCTGAAGCTAACTCAAG
ATGGAAAGTGAAACCACATGTGCCGTGACCTTTAGGTTTTATGAGTAGACAGTGTTCATT
TGATTTTCTACAGAAATAATATAAATTATTCTTTAGGTTTAAAAAAGAGCACTCATAATG

Fig. 9D

CAATATGTGAATAATCAGTGAGGTTGATTTTTCTTTTTTCCTACCGTTTCATAGTCTTTG
TCTAACTGCTAGTAACCCTACCGAGTTTTATATATGAGTGGGATACTCAATCTGGCCTTA
AAAAGATACACAAAGATGGGCTGTGGGTCCCTGGAAAGGGGGAGAGTTGCCCTTTACAGA
ATCACTCGAGCCCTTTCCAGCACTGTTGGTCTGATGAACAAGGTTGTTTTACCTTATTTT
CTCTTGGAACATATCTGAAAACCTTCCCCACAAATAACTTGTCACACCTTTTGTTTCATT
CTGAGTCTTTAGTTTTAGTCATGGGCTTTCTTCACCTGCTCTAGGTGCAAAGGCATGTTG
GGAAAGAGATGGATGTTGGGGAGGAAGAGAGGAGATGGATTTCAGTTGGGAGTTAGGAGG
AGAGTAGGTGAGATGATCAGACACCGGAGTTCAACGTCCCAGCAGTCTTGGTAAAAGGAG
GGAGCCTGCTGAGCCAGGAGGGAGAAAAGAAGATTGACCAGCTTGCTAGAAAAATACTTA
GCTTTTCTTTTTCTTTTTTTGTGGAGGGGGGACGGAGAGGAACAAGGATGGGGAGGTAGG
AATGAGGTATAGAAAAGAGATAGCATCTTCTTTGGCACAAGACTAGTGGCTTACCGCTTA
CCTTAGAGTTTTGTTTTTTTTTTTTCAAACCCATCAAAATCTACTTATTTATGAATCCAA
GGGGTGGCAGCATCACTCTGTTCTAGCATTCTTTGTGGAGATGGTCTGGTGCCTAGCTGG
GAGTGAGCAGCAGCCCATCCCCTGTTCACTTTCTCTAGCCCATCATTACCTGTGAACTGC
AGTGGGGCAGTCATGGCAAATAGAATTGGGCTGGGGTTTCTCCTTCTTTTCAGTTCATTG
TTTGCCCTGCTAGGAATTAGAAGACAGACACCATGTCCCAGGACAGTGTTACTTCTTCTG
CATGATGTGTGGTAGACTCCCTTTGCTGGCTTGTGCAGTGATACTGAGAAAATACATGAA
CAGAAACTGCCCAGGTGGAACAGCACGTAACCTAGTGAGTGACTGTACTCCTTTCTAGGA
ATGCTGATTCAGAGTGCACCTCTTTGACTAGGTCCCAGGATCCCCTTGTCCCTGGAGTAG
GGACTAACTATAGCACAAAGTAATATGTGCCAATGCTATTTGTGAAATGTTTGGTCTTTC
TAAACGACTAAAGGATTTGTTGGGTTTTTGCTTAAGTTTTGAACCAAATCCTAGAGCCAG
CTGATAATATTTAATAATCTGGAGGAGAGAATAATGATGTACCAATAAGTGGAGATTCCT
CCTTATGATGTATGCTAGGTTATGGAAGATGTAAAATATTCAACTTTTTCCTCCTTTTTT
TGGACTTTGTATTTTACTGCATGTTTTCTTCATTTTTAATCAATAAAGAGTAAATTGTCA
AAAAAAAAAAAAAAAA

SEQ ID NO: 4 STLK5 HUMAN

CTCATCTGTACACACTTCATGGATGGCATGAATGAGCTGGCGATTGCTTACATCCTGCAG
GGGGTGCTGAAGGCCCTCGACTACATCCACCACATGGGATATGTACACAGGAGTGTCAAA
GCCAGCCACATCCTGATCTCTGTGGATGGGAAGGTCTACCTGTCTGGTTTGCGCAGCAAC
CTCAGCATGATAAGCCATGGGCAGCGGCAGCGAGTGGTCCACGATTTTCCCAAGTACAGT
GTCAAGGTTCTGCCGTGGCTCAGCCCCGAGGTCCTCCAGCAGAATCTCCAGGGTTATGAT
GCCAAGTCTGACATCTACAGTGTGGGAATCACAGCCTGTGAACTGGCCAACGGCCATGTC
CCCTTTAAGGATATGCCTGCCACCCAGATGCTGCTAGAGAAACTGAACGGCACAGTGCCC
TGCCTGTTGGATACCAGCACCATCCCCGCTGAGGAGCTGACCATGAGCCCTTCGCGCTCA
GTGGCCAACTCTGGCCTGAGTGACAGCCTGACCACCAGCACCCCCCGGCCCTCCAACGGT
GACTCGCCCTCCCACCCCTACCACCGAACCTTCTCCCCCCACTTCCACCACTTTGTGGAG
CAGTGCCTTCAGCGCAACCCGGATGCCAGGCCCAGTGCCAGCACCCTCCTGAACCACTCT

Fig. 9E

TTCTTCAAGCAGATCAAGCGACGTGCCTCAGAGGCTTTGCCCGAATTGCTTCGTCCTGTC
ACCCCCATCACCAATTTTGAGGGCAGCCAGTCTCAGGACCACAGTGGAATCTTTGGCCTG
GTAACAAACCTGGAAGAGCTGGAGGTGGACGATTGGGAGTTCTGAGCCTCTGCAAACTGT
GCGCATTCTCCAGCCAGGGATGCAGAGGCCACCCAGAGGCCCTTCCTGAGGGCCGGCCAC
ATTCCCGCCCTCCTGGGCAGATTGGGTAGAAAGGACATTCTTCCAGGAAAGTTGACTGCT
GACTGATTGGGAAAGAAAATCCTGGAGAGATACTTCACTGCTCCAAGGCTTTTGAGACAC
AAGGGAATCTCAACAACCAGGGATCAGGAGGGTCCAAAGCCGACATTCCCAGTCCTGTGA
GCTCAGGTGACCTCCTCCGCAGAAGAGAGATGCTGCTCTGGCCCTGGGAGCTGAATTCCA
AGCCCAGGGTTTGGCTCCTTAAACCCGAGGACCGCCACCTCTTCCCAGTGCTTGCGACCA
GCCTCATTCTATTTAACTTTGCTCTCAGATGCCTCAGATGCTATAGGTCAGTGAAAGGGC
AAGTAGTAAGCTGCCTGCCTCCCTTCCCTCAGACCTCTCCCTCATAATTCCAGAGAAGGG
CATTTCTGTCTTTTTAAGCACAGACTAAGGCTGGAACAGTCCATCCTTATCCCTCTTCTG
GCTTGGGCCCTGACACCTAAGTCTTTCCCACGGTTTATGTGTGTGCCTCATTCCTTTCCC
ACCAAGAATCCATCTTAGCGCCTCCTGCCAGCTGCCCTGGTGCTTTCTCCAAGGGCCATC
AGTGTCTTGCCTAGCTTGAGGGCTTAAGTCCTTATGCTGTGTTAGTTTCGTTGTCAGAAC
AAATTAAAATTTTCAGAGACGCTG

SEQ ID NO: 9 ZC1 HUMAN
GAGACCATGGCGAACGACTCTCCCGCGAAAAGTCTGGTGGACATCGACCTCTCCTCCCTG
CGGGATCCTGCTGGGATTTTTGAGCTGGTGGAAGTGGTTGGAAATGGCACCTATGGACAA
GTCTATAAGGGTCGACATGTTAAAACGGGTCAGTTGGCAGCCATCAAAGTTATGGATGTC
ACTGAGGATGAAGAGGAAGAAATCAAACTGGAGATAAATATGCTAAAGAAATACTCTCAT
CACAGAAACATTGCAACATATTATGGTGCTTTCATCAAAAAGAGCCCTCCAGGACATGAT
GACCAACTCTGGCTTGTTATGGAGTTCTGTGGGGCTGGGTCCATTACAGACCTTGTGAAG
AACACCAAAGGGAACACACTCAAAGAAGACTGGATCGCTTACATCTCCAGAGAAATCCTG
AGGGGACTGGCACATCTTCACATTCATCATGTGATTCACCGGGATATCAAGGGCCAGAAT
GTGTTGCTGACTGAGAATGCAGAGGTGAAACTTGTTGACTTTGGTGTGAGTGCTCAGCTG
GACAGGACTGTGGGGCGGAGAAATACGTTCATAGGCACTCCCTACTGGATGGCTCCTGAG
GTCATCGCCTGTGATGAGAACCCAGATGCCACCTATGATTACAGAAGTGATCTTTGGTCT
TGTGGCATTACAGCCATTGAGATGGCAGAAGGTGCTCCCCCTCTCTGTGACATGCATCCA
ATGAGAGCACTGTTTCTCATTCCCAGAAACCCTCCTCCCCGGCTGAAGTCAAAAAAATGG
TCGAAGAAGTTTTTTAGTTTTATAGAAGGGTGCCTGGTGAAGAATTACATGCAGCGGCCC
TCTACAGAGCAGCTTTTGAAACATCCTTTTATAAGGGATCAGCCAAATGAAAGGCAAGTT
AGAATCCAGCTTAAGGATCATATAGATCGTACCAGGAAGAAGAGAGGCGAGAAAGATGAA
ACTGAGTATGAGTACAGTGGGAGTGAGGAAGAAGAGGAGGAAGTGCCTGAACAGGAAGGA
GAGCCAAGTTCCATTGTGAACGTGCCTGGTGAGTCTACTCTTCGCCGAGATTTCCTGAGA
CTGCAGCAGGAGAACAAGGAACGTTCCGAGGCTCTTCGGAGACAACAGTTACTACAGGAG
CAACAGCTCCGGGAGCAGGAAGAATATAAAAGGCAACTGCTGGCAGAGAGACAGAAGCGG

Fig. 9F

ATTGAGCAGCAGAAAGAACAGAGGCGACGGCTAGAAGAGCAACAAAGGAGAGAGCGGGAA
GCTAGAAGGCAGCAGGAACGTGAACAGCGAAGGAGAGAACAAGAAGAAAAGAGGCGTCTA
GAGGAGTTGGAGAGAAGGCGCAAAGAAGAAGAGGAGAGGAGACGGGCAGAAGAAGAAAAG
AGGAGAGTTGAAAGAGAACAGGAGTATATCAGGCGACAGCTAGAAGAGGAGCAGCGGCAC
TTGGAAGTCCTTCAGCAGCAGCTGCTCCAGGAGCAGGCCATGTTACTGGAGTGCCGATGG
CGGGAGATGGAGGAGCACCGGCAGGCAGAGAGGCTCCAGAGGCAGTTGCAACAAGAACAA
GCATATCTCCTGTCTCTACAGCATGACCATAGGAGGCCGCACCCGCAGCACTCGCAGCAG
CCGCCACCACCGCAGCAGGAAAGGAGCAAGCCAAGCTTCCATGCTCCCGAGCCCAAAGCC
CACTACGAGCCTGCTGACCGAGCGCGAGAGGTGGAAGATAGATTTAGGAAAACTAACCAC
AGCTCCCCTGAAGCCCAGTCTAAGCAGACAGGCAGAGTATTGGAGCCACCAGTGCCTTCC
CGATCAGAGTCTTTTTCCAATGGCAACTCCGAGTCTGTGCATCCCGCCCTGCAGAGACCA
GCGGAGCCACAGGTTCCTGTGAGAACAACATCTCGCTCCCCTGTTCTGTCCCGTCGAGAT
TCCCCACTGCAGGGCAGTGGGCAGCAGAATAGCCAGGCAGGACAGAGAAACTCCACCAGT
ATTGAGCCCAGGCTTCTGTGGGAGAGAGTGGAGAAGCTGGTGCCCAGACCTGGCAGTGGC
AGCTCCTCAGGGTCCAGCAACTCAGGATCCCAGCCCGGGTCTCACCCTGGGTCTCAGAGT
GGCTCCGGGGAACGCTTCAGAGTGAGATCATCATCCAAGTCTGAAGGCTCTCCATCTCAG
CGCCTGGAAAATGCAGTGAAAAAACCTGAAGATAAAAAGGAAGTTTTCAGACCCCTCAAG
CCTGCTGATCTGACCGCACTGGCCAAAGAGCTTCGAGCAGTGGAAGATGTACGGCCACCT
CACAAAGTAACGGACTACTCCTCATCCAGTGAGGAGTCGGGGACGACGGATGAGGAGGAC
GACGATGTGGAGCAGGAAGGGGCTGACGAGTCCACCTCAGGACCAGAGGACACCAGAGCA
GCGTCATCTCTGAATTTGAGCAATGGTGAAACGGAATCTGTGAAAACCATGATTGTCCAT
GATGATGTAGAAAGTGAGCCGGCCATGACCCCATCCAAGGAGGGCACTCTAATCGTCCGC
CGGACTCAGTCCGCTAGTAGCACACTCCAGAAACACAAATCTTCCTCCTCCTTTACACCT
TTTATAGACCCCAGATTACTACAGATTTCTCCATCTAGCGGAACAACAGTGACATCTGTG
GTGGGATTTTCCTGTGATGGGATGAGACCAGAAGCCATAAGGCAAGATCCTACCCGGAAA
GGCTCAGTGGTCAATGTGAATCCTACCAACACTAGGCCACAGAGTGACACCCCGGAGATT
CGTAAATACAAGAAGAGGTTTAACTCTGAGATTCTGTGTGCTGCCTTATGGGGAGTGAAT
TTGCTAGTGGGTACAGAGAGTGGCCTGATGCTGCTGGACAGAAGTGGCCAAGGGAAGGTC
TATCCTCTTATCAACCGAAGACGATTTCAACAAATGGACGTACTTGAGGGCTTGAATGTC
TTGGTGACAATATCTGGCAAAAAGGATAAGTTACGTGTCTACTATTTGTCCTGGTTAAGA
AATAAAATACTTCACAATGATCCAGAAGTTGAGAAGAAGCAGGGATGGACAACCGTAGGG
GATTTGGAAGGATGTGTACATTATAAAGTTGTAAAATATGAAAGAATCAAATTTCTGGTG
ATTGCTTTGAAGAGTTCTGTGGAAGTCTATGCGTGGGCACCAAAGCCATATCACAAATTT
ATGGCCTTTAAGTCATTTGGAGAATTGGTACATAAGCCATTACTGGTGGATCTCACTGTT
GAGGAAGGCCAGAGGTTGAAAGTGATCTATGGATCCTGTGCTGGATTCCATGCTGTTGAT
GTGGATTCAGGATCAGTCTATGACATTTATCTACCAACACATATCCAGTGTAGCATCAAA
CCCCATGCAATCATCATCCTCCCCAATACAGATGGAATGGAGCTTCTGGTGTGCTATGAA
GATGAGGGGGTTTATGTAAACACATATGGAAGGATCACCAAGGATGTAGTTCTACAGTGG

Fig. 9G

GGAGAGATGCCTACATCAGTAGCATATATTCGATCCAATCAGACAATGGGCTGGGGAGAG
AAGGCCATAGAGATCCGATCTGTGGAAACTGGTCACTTGGATGGTGTGTTCATGCACAAA
AGGGCTCAAAGACTAAAATTCTTGTGTGAACGCAATGACAAGGTGTTCTTTGCCTCTGTT
CGGTCTGGTGGCAGCAGTCAGGTTTATTTCATGACCTTAGGCAGGACTTCTCTTCTGAGC
TGGTAGAAGCAGTGTGATCCAGGGATTACTGGCCTCCAGAGTCTTCAAGATCCTGAGAAC
TTGGAATTCCTTGTAACT

SEQ ID NO: 10 ZC2 HUMAN
GCTTTCGGGGAGGTCTATGAGGGTCGTCATGTCAAAACGGGCCAGCTTGCAGCCATCAAG
GTTATGGATGTCACAGGGGATGAAGAGGAAGAAATCAAACAAGAAATTAACATGTTGAAG
AAATATTCTCATCACCGGAATATTGCTACATACTATGGTGCTTTTATCAAAAAGAACCCA
CCAGGCATGGATGACCAACTTTGGTTGGTGATGGAGTTTTGTGGTGCTGGCTCTGTCACC
GACCTGATCAAGAACACAAAAGGTAACACGTTGAAAGAGGAGTGGATTGCATACATCTGC
AGGGAAATCTTACGGGGGCTGAGTCACCTGCACCAGCATAAAGTGATTCATCGAGATATT
AAAGGGCAAAATGTCTTGCTGACTGAAAATGCAGAAGTTAAACTAGTGGACTTTGGAGTC
AGTGCTCAGCTTGATCGAACAGTGGGCAGGAGGAATACTTTCATTGGAACTCCCTACTGG
ATGGCACCAGAAGTTATTGCCTGTGATGAAAACCCAGATGCCACATATGATTTCAAGAGT
GACTTGTGGTCTTTGGGTATCACCGCCATTGAAATGGCAGAAGGTGCTCCCCCTCTCTGT
GACATGCACCCCATGAGAGCTCTCTTCCTCATCCCCCGGAATCCAGCGCCTCGGCTGAAG
TCTAAGAAGTGGTCAAAAAAATTCCAGTCATTTATTGAGAGCTGCTTGGTAAAGAATCAC
AGCCAGCGACCAGCAACAGAACAATTGATGAAGCATCCATTTATACGAGACCAACCTAAT
GAGCGACAGGTCCGCATTCAACTCAAGGACCATATTGATAGAACAAAGAAGAAGCGAGGA
GAAAAAGATGAGACAGAGTATGAGTACAGTGGAAGTGAGGAAGAAGAGGAGGAGAATGAC
TCAGGAGAGCCCAGCTCCATCCTGAATCTGCCAAGGGAGTCGACGCTGCGGAGGGACTTT
CTGAGGCTGCAGCTGGCCAACAAGGAGCGTTCTGAGGCCCTACGGAGGCAGCAGCTGGAG
CAGCAGCAGCGGGAGAATGAGGAGCACAAGCGGCAGCTGCTGGCCGAGCGTCAGAAGCGC
ATCGAGGAGCAGAAAGAGCAGAGGCGGCGGCTGGAGGAGCAACAAAGGCGAGAGAAGGAG
CTGCGGAAGCAGCAGGAGAGGGAGCAGCGCCGGCACTATGAGGAGCAGATGCGCCGGGAG
GAGGAGAGGAGGCGTGCGGAGCATGAACAGGAATATAAGCGCAAACAATTGGAAGAACAG
AGACAAGCAGAAAGACTGCAGAGGCAGCTAAAGCAAGAAAGAGACTACTTAGTTTCCCTT
CAGCATCAGCGGCAGGAGCAGAGGCCTGTGGAGAAGAAGCCACTGTACCATTACAAAGAA
GGAATGAGTCCTAGTGAGAAGCCAGCATGGGCCAAGGAGGTAGAAGAACGGTCAAGGCTC
AACCGGCAAAGTTCCCCTGCCATGCCTCACAAGGTTGCCAACAGGATATCTGACCCCAAC
CTGCCCCCAAGGTCGGAGTCCTTCAGCATTAGTGGAGTTCAGCCTGCTCGAACACCCCCC
ATGCTCAGACCAGTCGATCCCCAGATCCCACATCTGGTAGCTGTAAAATCCCAGGGACCT
GCCTTGACCGCCTCCCAGTCAGTGCACGAGCAGCCCACAAAGGGCCTCTCTGGGTTTCAG
GAGGCTCTGAACGTGACCTCCCACCGCGTGGAGATGCCACGCCAGAACTCAGATCCCACC
TCGGAAAATCCTCCTCTCCCCACTCGCATTGAAAAGTTTGACCGAAGCTCTTGGTTACGA

Fig. 9H

CAGGAAGAAGACATTCCACCAAAGGTGCCTCAAAGAACAACTTCTATATCCCCAGCATTA
GCCAGAAAGAATTCTCCTGGGAATGGTAGTGCTCTGGGACCCAGACTAGGATCTCAACCC
ATCAGAGCAAGCAACCCTGATCTCCGGAGAACTGAGCCCATCTTGGAGAGCCCCTTGCAG
AGGACCAGCAGTGGCAGTTCCTCCAGCTCCAGCACCCCTAGCTCCCAGCCCAGCTCCCAA
GGAGGCTCCCAGCCTGGATCACAAGCAGGATCCAGTGAACGCACCAGAGTTCGAGCCAAC
AGTAAGTCAGAAGGATCACCTGTGCTCCCCCATGAGCCTGCCAAGGTGAAACCAGAAGAA
TCCAGGGACATTACCCGGCCCAGTCGACCAGCTAGCTACAAAAAAGCTATAGATGAGGAT
CTGACGGCATTAGCCAAAGAACTAAGAGAACTCCGGATTGAAGAAACAAACCGCCCAATG
AAGAAGGTGACTGATTACTCCTCCAGTGAGGAGTCAGAAAGTAGCGAGGAAGAGGAG
GAAGATGGAGAGAGCGAGACCCATGATGGGACAGTGGCTGTCAGCGACATACCCAGACTG
ATACCAACAGGAGCTCCAGGCAGCAACGAGCAGTACAATGTGGGAATGGTGGGGACGCAT
GGGCTGGAGACCTCTCATGCGGACAGTTTCAGCGGCAGTATTTCAAGAGAAGGAACCTTG
ATGATTAGAGAGACGTCTGGAGAGAAGAAGCGATCTGGCCACAGTGACAGCAATGGCTTT
GCTGGCCACATCAACCTCCCTGACCTGGTGCAGCAGAGCCATTCTCCAGCTGGAACCCCG
ACTGAGGGACTGGGGCGCGTCTCAACCCATTCCCAGGAGATGGACTCTGGGACTGAATAT
GGCATGGGGAGCAGCACCAAAGCCTCCTTCACCCCCTTTGTGGACCCCAGAGTATACCAG
ACGTCTCCCACTGATGAAGATGAAGAGGATGAGGAATCATCAGCCGCAGCTCTGTTTACT
GGCGAACTTCTTAGGCAAGAACAGGCCAAACTCAATGAAGCAAGAAAGATTTCGGTGGTA
AATGTAAACCCAACCAACATTCGGCCTCATAGCGACACACCAGAAATCAGAAAATACAAG
AAACGATTCAACTCAGAAATACTTTGTGCAGCTCTGTGGGGTGTAAACCTTCTGGTGGGG
ACTGAAAATGGCCTGATGCTTTTGGACCGAAGTGGGCAAGGCAAAGTCTATAATCTGATC
AACCGGAGGCGATTTCAGCAGATGGATGTGCTAGAGGGACTGAATGTCCTTGTGACAATT
TCAGGAAAGAAGAATAAGCTACGAGTTTACTATCTTTCATGGTTAAGAAACAGAATACTA
CATAATGACCCAGAAGTAGAAAAGAAACAAGGCTGGATCACTGTTGGGGACTTGGAAGGC
TGTATACATTATAAAGTTGTTAAATATGAAAGGATCAAATTTTTGGTGATTGCCTTAAAG
AATGCTGTGGAAATATATGCTTGGGCTCCTAAACCGTATCATAAATTCATGGCATTTAAG
TCTTTTGCAGATCTCCAGCACAAGCCTCTGCTAGTTGATCTCACGGTAGAAGAAGGTCAA
AGATTAAAGGTTATTTTTGGTTCACACACTGGTTTCCATGTAATTGATGTTGATTCAGGA
AACTCTTATGATATCTACACACCATCTCATATTCAGGGCAATATCACTCCTCATGCTATT
GTCATCTTGCCTAAAACAGATGGAATGGAAATGCTTGTTTGCTATGAGGATGAGGGGGTG
TATGTAAACACCTATGGCCGGATAACTAAGGATGTGGTGCTCCAATGGGGAGAAATGCCC
ACGTCTGTGGCCTACATTCATTCCAATCAGATAATGGGCTGGGGCGAGAAAGCTATTGAG
ATCCGGTCAGTGGAAACAGGACATTTGGATGGAGTATTTATGCATAAGCGAGCTCAAAGG
TTAAAGTTTCTATGTGAAAGAAATGATAAGGTATTTTTTGCATCCGTGCGATCTGGAGGA
AGTAGCCAAGTGTTTTTCATGACCCTCAACAGAAATTCCATGATGAACTGGTAACAGAAG
AGCACTTGGCACTTATCTTCATGGCGTTATTTCTAATTTAAAAGAACATAACTCATGTGG
ACTTATGCCAGTCTAGAGGCAGAATCAGAAGGCTTGGTTGAACATATCGCTTTCCCTTTT
TCCTCTCCCTCCGCCCCTCCCAGTACAGTCCATCT

Fig. 9 I

SEQ ID NO: 11 ZC3 HUMAN

GCATTTGGGGAGGTGTATGAGGGTCGGCATGTCAAGACGGGGCAGCTGGCTGCCATCAAG
GTCATGGATGTCACGGAGGACGAGGAGGAAGAGATCAAACAGGAGATCAACATGCTGAAA
AAGTACTCTCACCACCGCAACATCGCCACCTACTACGGAGCCTTCATCAAGAAGAGCCCC
CCGGGAAACGATGACCAGCTCTGGCTGGTGATGGAGTTCTGTGGTGCTGGTTCAGTGACT
GACCTGGTAAAGAACACAAAAGGCAACGCCCTGAAGGAGGACTGTATCGCCTATATCTGC
AGGGAGATCCTCAGGGGTCTGGCCCATCTCCATGCCCACAAGGTGATCCATCGAGACATC
AAGGGGCAGAATGTGCTGCTGACAGAGAATGCTGAGGTCAAGCTAGTGGATTTTGGGGTG
AGTGCTCAGCTGGACCGCACCGTGGGCAGACGGAACACTTTCATTGGGACTCCCTACTGG
ATGGCTCCAGAGGTCATCGCCTGTGATGAGAACCCTGATGCCACCTATGATTACAGGAGT
GATATTTGGTCTCTAGGAATCACAGCCATCGAGATGGCAGAGGGAGCCCCCCCTCTGTGT
GACATGCACCCCATGCGAGCCCTCTTCCTCATTCCTCGGAACCCTCCGCCCAGGCTCAAG
TCCAAGAAGTGGTCTAAGAAGTTCATTGACTTCATTGACACATGTCTCATCAAGACTTAC
CTGAGCCGCCCACCCACGGAGCAGCTACTGAAGTTTCCCTTCATCCGGGACCAGCCCACG
GAGCGGCAGGTCCGCATCCAGCTTAAGGACCACATTGACCGATCCCGGAAGAAGCGGGGT
GAGAAAGAGGAGACAGAATATGAGTACAGCGGCAGCGAGGAGGAAGATGACAGCCATGGA
GAGGAAGGAGAGCCAAGCTCCATCATGAACGTGCCTGGAGAGTCGACTCTACGCCGGGAG
TTTCTCCGGCTCCAGCAGGAAAATAAGAGCAACTCAGAGGCTTTAAAACAGCAGCAGCAG
CTGCAGCAGCAGCAGCAGCGAGACCCCGAGGCACACATCAAACACCTGCTGCACCAGCGG
CAGCGGCGCATAGAGGAGCAGAAGGAGGAGCGGCGCCGCGTGGAGGAGCAACAGCGGCGG
GAGCGGGAGCAGCGGAAGCTGCAGGAGAAGGAGCAGCAGCGGCGGCTGGAGGACATGCAG
GCTCTGCGGCGGGAGGAGGAGCGGCGGCAGGCGGAGCGCGAGCAGGAATATATTCGTCAC
AGGCTAGAGGAGGAGCAGCGACAGCTCGAGATCCTTCAGCAACAGCTGCTCCAGGAACAG
GCCCTGCTGCTGGAATACAAGCGGAAGCAGCTGGAGGAGCAGCGGCAGTCAGAACGTCTC
CAGAGGCAGCTGCAGCAGGAGCATGCCTACCTCAAGTCCCTGCAGCAGCAGCAACAGCAG
CAGCAGCTTCAGAAACAACAGCAGCAGCAGCTCCTGCCTGGGGACAGGAAGCCCCTGTAC
CATTATGGTCGGGGCATGAATCCCGCTGACAAACCAGCCTGGGCCCGAGAGGTAGAAGAG
AGAACAAGGATGAACAAGCAGCAGAACTCTCCCTTGGCCAAGAGCAAGCCAGGCAGCACG
GGGCCTGAGCCCCCCATCCCCCAGGCCTCCCCAGGGCCCCCAGGACCCCTTTCCCAGACT
CCTCCTATGCAGAGGCCGGTGGAGCCCCAGGAGGGACCGCACAAGAGCCTGGTGGCACAC
CGGGTCCCACTGAAGCCATATGCAGCACCTGTACCCCGATCCCAGTCCCTGCAGGACCAG
CCCACCCGAAACCTGGCTGCCTTCCCAGCCTCCCATGACCCCGACCCTGCCATCCCCGCA
CCCACTGCCACGCCCAGTGCCCGAGGAGCTGTCATCCGCCAGAATTCAGACCCCACCTCT
GAAGGACCTGGCCCCAGCCCGAATCCCCCAGCCTGGGTCCGCCCAGATAACGAGGCCCCA
CCCAAGGTGCCTCAGAGGACCTCATCTATCGCCACTGCCCTTAACACCAGTGGGGCCGGA
GGGTCCCGGCCAGCCCAGGCAGTCCGTGCCAGACCTCGCAGCAACTCCGCCTGGCAAATC
TATCTGCAAAGGCGGGCAGAGCGGGGCACCCCAAAGCCTCCAGGGCCCCCTGCTCAGCCC
CCTGGCCCGCCCAACGCCTCTAGTAACCCCGACCTCAGGAGGAGCGACCCTGGCTGGGAA

Fig. 9J

CGCTCGGACAGCGTCCTTCCAGCCTCTCACGGGCACCTCCCCCAGGCTGGCTCACTGGAG
CGGAACCGCGTGGGAGTCTCCTCCAAACCGGACAGCTCCCCTGTGCTCTCCCCTGGGAAT
AAAGCCAAGCCCGACGACCACCGCTCACGGCCAGGCCGGCCCGCAGACTTTGTGTTGCTG
AAAGAGCGGACTCTGGACGAGGCCCCTCGGCCTCCCAAGAAGGCCATGGACTACTCGTCG
TCCAGCGAGGAGGTGGAAAGCAGTGAGGACGACGAGGAGGAAGGCGAAGGCGGGCCAGCA
GAGGGGAGCAGAGATACCCCTGGGGGCCGCGATGGGGATACAGACAGCGTCAGCACCATG
GTGGTCCACGACGTCGAGGAGATCACCGGGACCCAGCCCCCATACGGGGGCGGCACCATG
GTGGTCCAGCGCACCCCTGAAGAGGAGCGGAACCTGCTGCATGCTGACAGCAATGGGTAC
ACAAACCTGCCTGACGTGGTCCAGCCCAGCCACTCACCCACCGAGAACAGCAAAGGCCAA
AGCCCACCCTCGAAGGATGGGAGTGGTGACTACCAGTCTCGTGGGCTGGTAAAGGCCCCT
GGCAAGAGCTCGTTCACGATGTTTGTGGATCTAGGGATCTACCAGCCTGGAGGCAGTGGG
GACAGCATCCCCATCACAGCCCTAGTGGGTGGAGAGGGCACTCGGCTCGACCAGCTGCAG
TACGACGTGAGGAAGGGTTCTGTGGTCAACGTGAATCCCACCAACACCCGGGCCCACAGT
GAGACCCCTGAGATCCGGAAGTACAAGAAGCGATTCAACTCCGAGATCCTCTGTGCAGCC
CTTTGGGGGGTCAACCTGCTGGTGGGCACGGAGAACGGGCTGATGTTGCTGGACCGAAGT
GGGCAGGGCAAGGTGTATGGACTCATTGGGCGGCGACGCTTCCAGCAGATGGATGTGCTG
GAGGGGCTCAACCTGCTCATCACCATCTCAGGGAAAAGGAACAAACTGCGGGTGTATTAC
TTGTCCTGGCTCCGGAACAAGATTCTGCACAATGACCCAGAAGTGGAGAAGAAGCAGGGC
TGGACCACCGTGGGGGACATGGAGGGCTGCGGGCACTACCGTGTTGTGAAATACGAGCGG
ATTAAGTTCCTGGTCATCGCCCTCAAGAGCTCCGTGGAGGTGTATGCCTGGGCCCCCAAA
CCCTACCACAAATTCATGGCCTTCAAGTCCTTTGCCGACCTCCCCCACCGCCCTCTGCTG
GTCGACCTGACAGTAGAGGAGGGGCAGCGGCTCAAGGTCATCTATGGCTCCAGTGCTGGC
TTCCATGCTGTGGATGTCGACTCGGGGAACAGCTATGACATCTACATCCCTGTGCACATC
CAGAGCCAGATCACGCCCCATGCCATCATCTTCCTCCCCAACACCGACGGCATGGAGATG
CTGCTGTGCTACGAGGACGAGGGTGTCTACGTCAACACGTACGGGCGCATCATTAAGGAT
GTGGTGCTGCAGTGGGGGGAGATGCCTACTTCTGTGGCCTACATCTGCTCCAACCAGATA
ATGGGCTGGGGTGAGAAAGCCATTGAGATCCGCTCTGTGGAGACGGGCCACCTCGACGGG
GTCTTCATGCACAAACGAGCTCAGAGGCTCAAGTTCCTGTGTGAGCGGAATGACAAGGTG
TTTTTTGCCTCAGTCCGCTCTGGGGGCAGCAGCCAAGTTTACTTCATGACTCTGAACCGT
AACCGCATCATGAACTGGTGACGGGGCCCTGGGCTGGGGCTGTCCCACACTGGACCCAGC
TCTCCCCCTGCAGCCAGGCTTCCCGGGCCGCCCCTCTTTCCCCTCCCTGGGCTTTTGCTT
TTACTGGTTTGATTTCACTGGAGCCTGCTGGGAACGTGACCTCTGACCCCTGA

SEQ ID NO: 12 ZC4 HUMAN
CAATGTTAACCCACTCTATGTCTCTCCTGCATGTAAAAAACCACTAATCCACATGTATGA
AAAGGAGTTCACTTCTGAGATCTGCTGTGGTTCTTTGTGGGGAGTCAATTTGCTGTTGGG
AACCCGATCTAATCTATATCTGATGGACAGAAGTGGAAAGGCTGACATTACTAAACTTAT
AAGGCGAAGACCATTCCGCCAGATTCAAGTCTTAGAGCCACTCAATTTGCTGATTACCAT

Fig. 9K

CTCAGGTCATAAGAACAGACTTCGGGTGTATCATCTGACCTGGTTGAGGAACAAGATTTT
GAATAATGATCCAGAAAGTAAAAGAAGGCAAGAAGAAATGCTGAAGACAGAGGAAGCCTG
CAAAGCTATTGATAAGTTAACAGGCTGTGAACACTTCAGTGTCCTCCAACATGAAGAAAC
AACATATATTGCAATTGCTTTGAAATCATCAATTCACCTTTATGCATGGGCACCAAAGTC
CTTTGATGAAAGCACTGCTATTAAAGTATTTCCAACACTTGATCATAAGCCAGTGACAGT
TGACCTGGCTATTGGTTCTGAAAAAAGACTAAAGATTTTCTTCAGCTCAGCAGATGGATA
TCACCTCATCGATGCAGAATCTGAGGTTATGTCTGATGTGACCCTGCCAAAGAATCCCCT
GGAAATCATTATACCACAGAATATCATCATTTTACCTGATTGCTTGGGAATTGGCATGAT
GCTCACCTTCAATGCTGAAGCCCTCTCTGTGGAAGCAAATGAACAACTCTTCAAGAAGAT
CCTTGAAATGTGGAAAGACATACCATCTTCTATAGCTTTTGAATGTACACAGCGAACCAC
AGGATGGGGCCAAAAGGCCATTGAAGTGCGCTCTTTGCAATCCAGGGTTCTGGAAAGTGA
GCTGAAGCGCAGGTCAATTAAGAAGCTGAGATTCCTGTGCACCCGGGGTGACAAGCTGTT
CTTTACCTCTACCCTGCGCAATCACCACAGCCGGGTTTACTTCATGACACTTGGAAAACT
TGAAGAGCTCCAAAGCAATTATGATGTCTAAAAGTTTCCAGTGATTTATTACCACATTAT
AAACATCATGTATAGGCAGTCTGCATCTTCAGATTTCAGAGATTAAATGAGTATTCAGTT
TTATTTTTAGTAAAGATTAAATCCAAAACTTTACTTTTAATGTAGCACAGAATAGTTTTA
ATGAGAAATGCAGCTTTATGTATAAAATTAACTATAGCAAGCTCTAGGTACTCCAATGGT
GTACAATGTCTTTTGCACAAACTTTGTAACTTTTGTTACTGTGAATTCAAACATTACTCT
TTGGACAGTTTGGACAGTATCTGTATTCAGATTTTACAACATGGAGTAAAGAAACCTGTT
ATGAATTAGATTACAAGCAGCCTTCAAAAGAATTGGCACTGGGATAAGATTTTTCAGAAA
AGAAAAACATCGGCAAACT

SEQ ID NO: 17 KHS2 HUMAN
CCGCCATGAACCCCGGCTTCGATTTGTCCCGCCGGAACCCGCAGGAGGACTTCGAGCTGA
TTCAGCGCATCGGCAGCGGCACCTACGGCGACGTCTACAAGGCACGGAATGTTAACACTG
GTGAATTAGCAGCAATTAAAGTAATAAAATTGGAACCAGGAGAAGACTTTGCAGTTGTGC
AGCAAGAAATTATTATGATGAAAGACTGTAAACACCCAAATATTGTTGCTTATTTTGGAA
GCTATCTCAGGCGAGATAAGCTTTGGATTTGCATGGAGTTTTGTGGAGGTGGTTCTTTAC
AGGATATTTATCACGTAACTGGACCTCTGTCAGAACTGCAAATTGCATATGTTAGCAGAG
AAACACTGCAGGGATTATATTATCTTCACAGTAAAGGAAAAATGCACAGAGATATAAAGG
GAGCTAACATTCTATTAACGGATAATGGTCATGTGAAATTGGCTGATTTTGGAGTATCTG
CACAGATAACAGCTACAATTGCCAAACGGAAGTCTTTCATTGGCACACCATATTGGATGG
CTCCAGAAGTTGCAGCTGTTGAGAGGAAGGGGGGTTACAATCAACTCTGTGATCTCTGGG
CAGTGGGAATCACTGCCATAGAACTTGCAGAGCTTCAGCCTCCTATGTTTGACTTACACC
CAATGAGAGCATTATTTCTAATGACAAAAAGCAATTTTCAGCCTCCTAAACTAAAGGATA
AAATGAAATGGTCAAATAGTTTTCATCACTTTGTGAAAATGGCACTTACCAAAAATCCGA
AAAAAAGACCTACTGCTGAAAAATTATTACAGCATCCTTTTGTAACACAACATTTGACAC
GGTCTTTGGCAATCGAGCTGTTGGATAAAGTAAATAATCCAGATCATTCCACTTACCATG

Fig. 9L

ATTTCGATGATGATGATCCTGAGCCTCTTGTTGCTGTACCACATAGAATTCACTCAACAA
GTAGAAACGTGAGAGAAGAAAAAACACGCTCAGAGATAACCTTTGGCCAAGTGAAATTTG
ATCCACCCTTAAGAAAGGAGACAGAACCACATCATGAACTTCCCGACAGTGATGGTTTTT
TGGACAGTTCAGAAGAAATATACTACACTGCAAGATCTAATCTGGATCTGCAACTGGAAT
ATGGACAAGGACACCAAGGTGGTTACTTTTTAGGTGCAAACAAGAGTCTTCTCAAGTCTG
TTGAAGAAGAATTGCATCAGCGAGGACACGTCGCACATTTAGAAGATGATGAAGGAGATG
ATGATGAATCTAAACACTCAACTCTGAAAGCAAAAATTCCACCTCCTTTGCCACCAAAGC
CTAAGTCTATCTTCATACCACAGGAAATGCATTCTACTGAGGATGAAAATCAAGGAACAA
TCAAGAGATGTCCCATGTCAGGGAGCCCAGCAAAGCCATCCCAAGTTCCACCTAGACCAC
CACCTCCCAGATTACCCCCACACAAACCTGTTGCCTTAGGAAATGGAATGAGCTCCTTCC
AGTTAAATGGTGAACGAGATGGCTCATTATGTCAACAACAGAATGAACATAGAGGCACAA
ACCTTTCAAGAAAAGAAAAGAAAGATGTACCAAAGCCTATTAGTAATGGTCTTCCTCCAA
CACCTAAAGTGCATATGGGTGCATGTTTTTCAAAAGTTTTTAATGGGTGTCCCTTGAAAA
TTCACTGTGCATCATCATGGATAAACCCAGATACAAGAGATCAGTACTTGATATTTGGTG
CCGAAGAAGGGATTTATACCCTCAATCTTAATGAACTTCATGAAACATCAATGGAACAGC
TATTCCCTCGAAGGTGTACATGGTTGTATGTAATGAACAATTGCTTGCTATCAATATCTG
GTAAAGCTTCTCAGCTTTATTCCCATAATTTACCAGGGCTTTTTGATTATGCAAGACAAA
TGCAAAAGTTACCTGTTGCTATTCCAGCACACAAACTCCCTGACAGAATACTGCCAAGGA
AATTTTCTGTATCAGCAAAAATCCCTGAAACCAAATGGTGCCAGAAGTGTTGTGTTGTAA
GAAATCCTTACACGGGCCATAAATACCTATGTGGAGCACTTCAGACTAGCATTGTTCTAT
TAGAATGGGTTGAACCAATGCAGAAATTTATGTTAATTAAGCACATAGATTTTCCTATAC
CATGTCCACTTAGAATGTTTGAAATGCTGGTAGTTCCTGAACAGGAGTACCCTTTAGTTT
GTGTTGGTGTCAGTAGAGGTAGAGACTTCAACCAAGTGGTTCGATTTGAGACGGTCAATC
CAAATTCTACCTCTTCATGGTTTACAGAATCAGATACCCCACAGACAAATGTTACTCATG
TAACCCAACTGGAGAGAGATACCATCCTTGTATGCTTGGACTGTTGTATAAAAATAGTAA
ATCTCCAAGGAAGATTAAAATCTAGCAGGAAATTGTCATCAGAACTCACCTTTGATTTCC
AGATTGAATCAATAGTGTGCCTACAAGACAGTGTGCTAGCTTTCTGGAAACATGGAATGC
AAGGTAGAAGTTTTAGATCTAATGAGGTAACACAAGAAATTTCAGATAGCACAAGAATTT
TCAGGCTGCTTGGATCTGACAGGGTCGTGGTTTTGGAAAGTAGGCCAACTGATAACCCCA
CAGCAAATAGCAATTTGTACATCCTGGCGGGTCATGAAAACAGTTACTGAGAATTGTTGT
GCTTTGACAGTTAACTCTAGAAAGAAAGAACACTACCACTGCAACATTAATGGATGCTTG
AAGCTGTACAAAAGCTGCAGTAACCTGTCTTCAGTTACTTTGTAATTTATTGTGGCATGA
GATAAGATGGGGAAAATTTTGTTTTAAGTGGTATGGATATATTTAGCATATTGAACCACA
CAAGTGCTTAATTCATTGTTATGTAATCTTTGTACATATAGGCAGTATTTTTTCTGTGAA
ACTTCATATTGCTGAAGACATACACTAAGAATTTATGTAGATAATGTACTTTTATGAGAT
GTACAAGTAAGTGTCTTATCTGTACAGATGTAAATGTTGATGAAAATGCAATTGGGGTTA
ATATTTTAAGAATTCTTTAGTATATTCTTGGGTGTGGCTATATTACAAAATGGGATGCTG
GCAATGAAACAATACATTTAACACTATTGTATTTTTATTATATGTAATTTAGTAATATGA

Fig. 9M

ATATAAATCTTGTAACTTTTAAAATTGTAATGGAGGCTGTAATCATTTTATAATCTTTTT
AATTTTAATGCAAGTACACTGGTGTTTATATTTGCACAAAGTATTGATATGTGATGTATT
AAGTCACAAAAGTAAGCTGTGACATTGTCTATAAGCATTTGGCTCCACAAATGTATTTGG
ATTGTTTTCTATGTGAAGCAAACCAATTATAATTAACCACATGTTGTAGTAACTGGTCTT
TTTATATTTAAGCAGAATCCTGTAAGATTGCTTGTCTTTGCTTAAAAACAATACCTTTGA
ACATTTTTGAATCACAGAATAGCGGTACCATGATAGAATACTGCAATTGTGGTCAGAATT
ACAGTATGCACAAAGAATTAATTAGCATTATTAAAGAGTCCTCACTAAACATTTCATATG
ATCACACTGAAGAACTGTAACATTCCATAGAGTGAAGTGGTTCAAATTTCTCTTGGAATT
TTTACTTTTGTTGGCCTTATTTTATGATCCTTTTCATATTTCTTTTGACTTAGAGTATTA
ATACATGGCCAAAATAATTTAGTTACTACCTCATACAAACAATATAATGGTTACTACACA
TCACAGGAACTTAGTTTTGGTTTAAGTCATTTTTGATTGCTTTTTTCCAATGGAATATGT
ATATACCAGGTTTTAGCAAAATGCACACTTTTGGCTCTTTTTGGTATATGTTCTTTATAT
TTTAATGTGAGTATATACACTAAGAACAAACTAAATTGTGATTTATGATCTTCATTTATT
TTAATGATAATGGTTTTAAAATATGTTCCTGATTGTACATATTGTAAAATAAACATGTTT
TTT

SEQ ID NO: 19 SULU1 HUMAN
GGGAGGGTCCTTGTGGCGCCGGGCGGCGGGGTCCTGCGTGGAGAGTGGGACGCAACGCCG
AGACCGCGAGCAGAGGCTGCGCACAGCCGGATCCGGCACTCAGCGACCGGACCCAAGGAT
CCGCCGGGGAACAAGCCACAGGAGAGCGACTCAGGAACAAGTGTGGGAGAGGAAGCGGCG
GCGGCGGCGCCGGGCCCGGGGGTGGTGACAGCAGGTCTGAGGTTGCATCATAAATACAAA
GGACTGAAGTTATAAAAGAGAAAAGAGAAGTTTGCTGCTAAAATGAATCTGAGCAATATG
GAATATTTTGTGCCACACACAAAAAGGTACTGAAGATTTACCCCCCAAAAAAAATTGTCA
ATGAGAAATAAAGCTAACTGATATCAAAAAGCAGAGCCTGCTCTACTGGCCATCATGCGT
AAAGGGGTGCTGAAGGACCCAGAGATTGACGATCTATTCTACAAAGATGATCCTGAGGAA
CTTTTTATTGGTTTGCATGAAATTGGACATGGAAGTTTTGGAGCAGTTTATTTTGCTACA
AATGCTCACACCAATGAGGTGGTGGCAATTAAGAAGATGTCCTATAGTGGGAAGCAGACC
CATGAGAAATGGCAAGATATTCTTAAGGAAGTTAAATTTTTACGACAATTGAAGCATCCT
AATACTATTGAGTACAAAGGCTGTTACTTGAAAGAACACACTGCTTGGTTGGTGATGGAA
TATTGCTTAGGCTCAGCCTCTGATTTATTAGAAGTTCATAAAAAACCACTTCAGGAAGTG
GAGATCGCTGCCATTACTCATGGAGCCTTGCATGGACTAGCCTACCTACATTCTCATGCA
TTGATTCATAGGGATATTAAAGCAGGAAATATTCTTCTAACAGAGCCAGGTCAGGTAAAA
CTAGCTGATTTTGGATCTGCTTCAATGGCTTCTCCTGCCAACTCCTTCGTGGGCACACCT
TACTGGATGGCTCCAGAGGTGATCTTAGCTATGGATGAAGGACAGTATGATGGGAAAGTT
GATATTTGGTCACTTGGCATCACTTGTATTGAATTGGCGGAACGGAAGCCGCCCCTTTTC
AACATGAATGCAATGAGTGCCTTATATCACATTGCCCAGAATGACTCCCCAACGTTACAG
TCTAATGAATGGACAGACTCCTTTAGGAGATTTGTTGATTACTGCTTGCAGAAAATACCT
CAGGAAAGGCCAACATCAGCAGAACTATTAAGGCATGACTTTGTTCGACGAGACCGGCCA

Fig. 9N

CTACGTGTCCTCATTGACCTCATACAGAGGACAAAAGATGCAGTTCGTGAGCTAGATAAC
CTACAGTACCGAAAAATGAAAAAAATACTTTTCCAAGAGACACGGAATGGACCCTTGAAT
GAGTCACAGGAGGATGAGGAAGACAGTGAACATGGAACCAGCCTGAACAGGGAAATGGAC
AGCCTGGGCAGCAACCATTCCATTCCAAGCATGTCCGTGAGCACAGGCAGCCAGAGCAGC
AGTGTGAACAGCATGCAGGAAGTCATGGACGAGAGCAGTTCCGAACTTGTCATGATGCAC
GATGACGAAAGCACAATCAATTCCAGCTCCTCCGTCGTGCATAAGAAAGATCATGTATTC
ACAAGGGATGAGGCGGGCCACGGCGATCCCAGGCCTGAGCCGCGGCCTACCCAGTCAGTT
CAGAGCCAGGCCCTCCACTACCGGAACAGAGAGCGCTTTGCCACGATCAAATCAGCATCT
TTGGTTACACGACAGATCCATGAGCATGAGCAGGAGAACGAGTTGCGGGAACAGATGTCA
GGTTATAAGCGGATGCGGCGCCAGCACCAGAAGCAGCTGATCGCCCTGGAGAACAAGCTG
AAGGCTGAGATGGACGAGCACCGCCTCAAGCTACAGAAGGAGGTGGAGACGCATGCCAAC
AACTCGTCCATCGAGCTGGAGAAGCTGGCCAAGAAGCAAGTGGCTATCATAGAAAAGGAG
GCAAAGGTAGCTGCAGCAGATGAGAAGAAGTTCCAGCAACAGATCTTGGCCCAGCAGAAG
AAAGATTTGACAACTTTCTTAGAAAGTCAGAAGAAGCAGTATAAGATTTGTAAGGAAAAA
ATAAAAGAGGAAATGAATGAGGACCATAGCACACCCAAGAAAGAGAAGCAAGAGCGGATC
TCCAAACATAAAGAGAACTTGCAGCACACACAGGCTGAAGAGGAAGCCCACCTTCTCACT
CAACAGAGACTGTACTACGACAAAAATTGTCGTTTCTTCAAGCGGAAAATAATGATCAAG
CGGCACGAGGTGGAGCAGCAGAACATTCGGGAGGAACTAAATAAAAAGAGGACCCAGAAG
GAGATGGAGCATGCCATGCTAATCCGGCACGACGAGTCCACCCGAGAGCTAGAGTACAGG
CAGCTGCACACGTTACAGAAGCTACGCATGGATCTGATCCGTTTACAGCACCAGACGGAA
CTGGAAAACCAGCTGGAGTACAATAAGAGGCGAGAAAGAGAACTGCACAGAAAGCATGTC
ATGGGACTTCGGCAACAGCCAAAAAACTTAAAGGCCATGGAAATGCAAATTAAAAAACAG
TTTCAGGACACTTGCAAAGTACAGACCAAACAGTATAAAGCACTCAAGAATCACCAGTTG
GAAGTTACTCCAAAGAATGAGCACAAAACAATCTTAAAGACACTGAAAGATGAGCAGACA
AGAAAACTTGCCATTTTGGCAGAGCAGTATGAACAGAGTATAAATGAAATGATGGCCTCT
CAAGCGTTACGGCTAGATGAGGCTCAAGAAGCAGAATGCCAGGCCTTGAGGCTACAGCTC
CAGCAGGAAATGGAGCTGCTCAACGCCTACCAGAGCAAAATCAAGATGCAAACAGAGGCA
CAACATGAACGTGAGCTCCAGAAGCTAGAGCAGAGAGTGTCTCTGCGCAGAGCACACCTT
GAGCAGAAGATTGAAGAGGAGCTGGCTGCCCTTCAGAAGGAACGCAGCGAGAGAATAAAG
AACCTATTGGAAAGGCAAGAGCGAGAGATTGAAACTTTTGACATGGAGAGCCTCAGAATG
GGATTTGGGAATTTGGTTACATTAGATTTTCCTAAGGAGGACTACAGATGAGATTAAATT
TTTTGCCATTTACAAAAAAAAAAAAAAAAAAGAAAACAGAAAAAAATTCAGACCCTGCAA
AACCACATTCCCCATTTTAACGGCGTTGCTCTCACTCTCTCTCTCTTACTCTTACTG
ACATCGTGTCGGACTAGTGCCTGTTTATTCTTACTCCATCAGGGGCCCCCTTCCTCCCCC
CGTGTCAACTTTCAGTGCTGGCCAAAACCTGGCCGTCTCTTCTATTCACAGTACACGTCA
CAGTATTGATGTGATTCAAAATGTTTCAGTGAAAACTTTGGAGACAGTTTTAACAAAACC
AATAAACCAACAACAAAAAAAGTGGATGTATATTGCTTTAAGCAATCACTCATTACCACC
AATCTGTGAAAGTAAAGCAAAAAATAATAATAAATGCCAAGGGGGAGAGAGACACAA

Fig. 9 O

TATCCGCAGCCTTACACCTTAACTAGCTGCTGCATTATTTTATTTTATTTTATTTTTTTG
GTATTTATTCATCAGGAATAAAAAAAACAAAGTTTTATTAAAGATTGAAAATTTGATACA
TTTTACAGAAACTAATTGTGATGTACATATCAGTGGTGACATATTATTACTTTTTTGGGG
ACGGGGGGTGGGTGGGGTGAAGAGATCTTGTGATTTTTAAGAACCTGCTGGCAAGAGTT
AACTTGTCTTCAGCATATTCTGATTGTATCATAATCATTTTCTGCTGTTGCAGAGGATGT
GAATACACTTAAGGAGCTCACAGAATCCCAGTAGCACAAATTGGGCTTTGGCAAATCGTG
TATTTTGTGTATAGAAGGAATTTAAGGAGAGGTATTACTTATTTTCATATTGTATTTTAA
CTGTTTCTCTGATCAAATTTTTTTACTTCCTCCTCCTGTTCCTCCCCACCTCCCTCCTTT
TCCAGTTCAGTATTTGGAGTTCAACACTGTCTCTCAATCAGATCATCTTGATCTTTTTCT
TTATCTCCCTTCCCCTTCCTAAGTCCCATTTCTTGGTCATAAATATTGCATTATTCACAC
TTTCAAACTGTGTATTTTCTTACAATAAAAAATGATGAAAAAAAAAAAAAAAAAAA

SEQ ID NO: 20 SULU3 HUMAN

TATTGAATTGGCGGAACGGAAGCCTCCTTTATTTAATATGAATGCAATGAGTGCCTTATA
TCACATAGCCCAAAATGAATCCCCTACACTACAGTCTAATGAATGGTCTGATTATTTTCG
CAACTTTGTAGATTCTTGCCTCCAGAAAATCCCTCAAGATCGACCTACATCAGAGGAACT
TTTAAAGCACATATTTGTTCTTCGGGAGCGCCCTGAAACCGTGTTAATAGATCTCATTCA
GAGGACAAAGGATGCAGTAAGAGAGCTGGACAATCTGCAGTATCGAAAGATGAAGAAACT
CCTTTTCCAGGAGGCACATAATGGACCAGCAGTAGAAGCACAGGAAGAAGAAGAGGAACA
AGATCATGGTGTTGGCCGGACAGGAACAGTTAATAGTGTTGGAAGTAATCAATCCATTCC
CAGCATGTCCATCAGTGCCAGCAGCCAAAGCAGTAGTGTTAACAGTCTTCCAGATGTCTC
AGATGACAAGAGTGAGCTAGACATGATGGAGGGAGACCACACAGTGATGTCTAACAGTTC
TGTTATCCATTTAAAACCAGAGGAAGAAAATTACAGAGAAGAGGGAGATCCTAGAACAAG
AGCATCAGATCCACAATCTCCACCCCAAGTATCTCGTCACAAATCACACTATCGTAATCG
AGAACACTTTGCTACTATACGGACAGCATCACTGGTTACGAGGCAAATGCAAGAACATGA
GCAGGACTCTGAGCTTAGAGAACAAATGTCTGGCTATAAGCGAATGAGGCGACAACATCA
AAAGCAACTGATGACTCTGGAAAACAAGCTAAAGGCTGAGATGGATGAACATCGCCTCAG
ATTAGACAAAGATCTTGAAACTCAGCGTAACAATTTTGCTGCAGAAATGGAGAAACTTAT
CAAGAAACACCAGGCTGCCATGGAGAAAGAGGCTAAAGTGATGTCCAATGAAGAGAAAAA
ATTTCAGCAACATATTCAGGCCCAACAGAAGAAAGAACTGAATAGTTTTCTCGAGTCCCA
GAAAAGAGAGTATAAACTTCGAAAAGAGCAGCTTAAAGAGGAGCTAAATGAAAACCAGAG
TACCCCCAAAAAAGAAAAACAGGAGTGGCTTTCAAAGCAGAAGGAGAATATACAGCATTT
CCAAGCAGAAGAAGAAGCTAACCTTCTTCGACGTCAAAGACAATACCTAGAGCTGGAATG
CCGTCGCTTCAAGAGAAGAATGTTACTTGGGCGTCATAACTTAGAGCAGGACCTTGTCAG
GGAGGAGTTAAACAAAAGACAGACTCAGAAGGACTTAGAGCATGCCATGCTACTCCGACA
GCATGAATCTATGCAAGAACTGGAGTTCCGCCACCTCAACACAATTCAGAAGATGCGCTG
TGAGTTGATCAGATTACAGCATCAAACTGAGCTCACTAACCAGCTGGAATATAATAAGCG
AAGAGAACGAGAACTAAGACGAAAGCATGTCATGGAAGTTCGACAACAGCCTAAGAGTTT

Fig. 9P

GAAGTCTAAAGAACTCCAAATAAAAAAGCAGTTTCAGGATACCTGCAAAATCCAAACCAG
ACAGTACAAAGCATTAAGAAATCACCTGCTGGAGACTACACCAAAGAGTGAGCACAAAGC
TGTTCTGAAACGGCTCAAGGAGGAACAGACCCGGAAATTAGCTATCTTGGCTGAGCAGTA
TGATCACAGCATTAATGAAATGCTCTCCACACAAGCCCTGCGTTTGGATGAAGCACAGGA
AGCAGAGTGCCAGGTTTTGAAGATGCAGCTGCAGCAGGAACTGGAGCTGTTGAATGCGTA
TCAGAGCAAAATCAAGATGCAAGCTGAGGCACAACATGATCGAGAGCTTCGCGAGCTTGA
ACAGAGGGTCTCCCTCCGGAGGGCACTCTTAGAACAAAAGATTGAAGAAGAGATGTTGGC
TTTGCAGAATGAGCGCACAGAACGAATACGAAGCCTGTTGGAACGTCAAGCCAGAGAGAT
TGAAGCTTTTGACTCTGAAAGCATGAGACTAGGTTTTAGTAATATGGTCCTTTCTAATCT
CTCCCCTGAGGCATTCAGCCACAGCTACCCGGGAGCTTCTGGTTGGTCACACAACCCTAC
TGGGGGTCCAGGACCTCACTGGGGTCATCCCATGGGTGGCCCACCACAAGCTTGGGGCCA
TCCAATGCAAGGTGGACCCCAGCCATGGGGTCACCCTTCAGGGCCAATGCAAGGGGTACC
TCGAGGTAGCAGTATGGGAGTCCGCAATAGCCCCCAGGCTCTGAGGCGGACAGCTTCTGG
GGGACGGACGGAGCAGGGCATGAGCAGAAGCACGAGTGTCACTTCACAAATATCCAATGG
GTCACACATGTCTTATACATAACTTAATAATTGAGAGTGGCAATTCCGCTGGAGCTGTCT
GCCAAAAGAAACTGCCTACAGACATCATCACAGCAGCCTCCTCACTTGGGTACTACAGTG
TGGAAGCTGAGTGCATATGGTATATTTATTCATTTTTGTAAAGCGTTCTGTTTTGTGTT
TACTAATTGGGATGTCATAGTACTTGGCTGCCGGGTTTGTTTGTTTTTGGGGAAATTTTG
AAAAGTGGAGTTGATATTAAAAATAAATGTGTATGTGTGTACATATATATACACACACAT
ACACATATATTATGCATGTGGTGAAAAGAATTGGCTAGATAGGGGATTTTTCTGAACACT
GCAAAAATAGAACGTAGCAAAATGGCTTCAGTTATCACTTTTGGGTGTCTGTATCCTAAG
AAGTTTCTGAAAAGATCTAAAGCCTTTTTATCCCATATCCCAAATTCTTATGAGCCACTC
ACAGCAGGCAGCATATGTTGAAATAAGTTATTACTGGTACACACCTGCATTGCCTCACCA
GTGTATTTATTTGTTATTAAATTGATCTGACTTCTCAGCCTCATTTGGACTAAAAAAAGA
AAGCAGAAATCCATGAACACATTGCTTCTCGGCCTTTTGGCTAAGATCAAGTGTAGAAAT
CCATGAACACTAAAGGACTTCATTGATTTTTTCAGAGAGTAGAAAACAACTTAGTTTTTC
TTTTTTCCTGAATGCGTCATAGGCTTGTGAGTGATTTTTGTCCATTCAATTGTGCCTTCT
TTGTATTATGATAAGATGGGGGTACTTAAGGAGATCACAAGTTGTGTGAGGATTGCATTA
ACAAACCTATGAGCCTTCAATGGGGAAGACCAGAAGGGTGAGAGGGGCCCTGAAAGTTCA
TATGGTGGGTATGTCCCGCAGCAGAGTGAGGAGATGAAGCTTACGTGTCCTGACGTTTTG
TTGCTTATACTGTGATATCTCATCCTAGCTAAGCTCTATAATGCCCAAGACCCCAAACAG
TACTTTTACTTTGTTTGTACAAAAACAAAGACATATAGCCAATACAAATCAAATGCCGGA
GGTGTTTGATGCCATATTTGCAAATTGCCATCTATTGAAATTCTCGTCACACTACATAGA
CATAATTGTTATCTCCTTTTGGCTTATGTGATTTTCTGTTTACAAGTAGAATAGCCAATT
ATTTAAATGTTTAGTTGCCACAGTGAACCAGGAGTCACTGAGCCAATGACTTTACCAGCT
GCTGACTAATCTTCATCACCACTGTAGATTTTGCTGCATGTGCAGGTCCTCTATTTTTAA
TTGCTGTTTTCGTTGCTGCAGTACTTTACAAACTTCTAGTTCGTTGAGACTTAGTGACCA
TTTGGCATCAAGTTAACATCACACAATAGGAAACACCACTTCCACAAGTCTCAAGCCTCA

Fig. 9Q

GTGCTAAAGTACTACTGAAAAGGAACTAGGAAGTTTGGCCAATT

SEQ ID NO: 21 SULU3 MURINE
GCAGGATGCCATCAACTAACAGAGCAGGCAGTCTAAAGGACCCTGAAATTGCAGAGCTCT
TCTTCAAAGAAGATCCGGAAAAGCTCTTCACAGATCTCAGAGAAATCGGCCATGGGAGCT
TTGGAGCAGTATATTTTGCACGAGATGTGCGTACTAATGAAGTGGTGGCCATCAAGAAAA
TGTCTTATAGTGGAAAGCAGTCTACTGAGAAATGGCAGGATATTATTAAGGAAGTCAAGT
TTCTACAAAGAATAAAACATCCCAACAGTATAGAATACAAAGGCTGCTATTTACGTGAAC
ACACAGCATGGCTTGTAATGGAATATTGTTTAGGATCTGCTTCAGATTTATTAGAAGTTC
ATAAAAAGCCATTACAAGAAGTGGAAATAGCAGCAATTACACATGGTGCTCTCCAGGGAC
TAGCTTATTTACATTCTCATACCATGATCCATAGAGATATCAAAGCAGGAAATATCCTTC
TGACAGAACCAGGCCAAGTGAAACTTGCTGACTTTGGATCTGCTTCCATGGCTTCCCCTG
CCAATTCTTTTGTGGGAACACCATATTGGATGGCCCCAGAAGTAATTTTAGCCATGGATG
AAGGACAGTATGATGGCAAAGTTGATGTATGGTCTCTTGGAATAACGTGTATTGAATTAG
CCGAGAGGAAGCCTCCTTTATTTAATATGAATGCAATGAGTGCCTTATATCACATAGCCC
AAAATGAATCCCCTACACTACAATCTAATATGAATGATTCTTGCCTCCAGAAAATCCCTC
AAGATCGCCCTACATCAGAGGAACTTTTAAAGCACATGTTTGTTCTTCGAGAGCGCCCTG
AAACAGTGTTAATAGATCTTATTCAAAGGACAAAGGATGCAGTAAGAGAGCTGGACAATC
TGCAGTATCGAAAGATGAAGAAACTCCTTTTCCAGGAGGCACATAATGGGCCAGCGGTAG
AAGCACAGGAAGAAGAGGAGGAGCAAGATCATGGTGTTGGCCGAACAGGAACAGTGAATA
GTGTTGGAAGCAATCAGTCTATCCCTAGTATGTCTATCAGTGCCAGCAGTCAAAGCAGCA
GTGTTAATAGTCTTCCAGATGCATCAGATGACAAGAGTGAGCTAGACATGATGGAGGGAG
ACCATACAGTGATGTCTAACAGTTCTGTCATCCACTTAAAACCTGAGGAGGAAAATTACC
AGGAAGAAGGAGATCCTAGAACAAGAGCATCAGACCCACAGTCTCCCCCTCAGGTGTCTC
GTCACAAGTCACATTATCGTAATAGAGAACACTTTGCAACCATACGAACAGCATCACTGG
TTACAAGACAGATGCAAGAACATGAGCAGGACTCTGAACTTAGAGAACAGATGTCTGGTT
ATAAGCGGATGAGGCGACAGCATCAAAAGCAGCTGATGACGCTGGAAAATAAACTGAAGG
CAGAGATGGACGAACATCGGCTCAGATTAGACAAAGATCTTGAAACTCAGCGTAACAATT
TCGCTGCAGAAATGGAGAAACTTATTAAGAAACACCAAGCTGCTATGGAAAAAGAGGCTA
AAGTGATGGCCAATGAGGAGAAAAAATTCCAGCAACACATTCAGGCTCAACAGAAAAAAG
AACTGAATAGCTTTTTGGAGTCTCAAAAAAGAGAATATAAACTTCGCAAAGAGCAGCTTA
AGGAGGAGCTGAATGAAAACCAGAGCACACCTAAAAAAGAAAAGCAGGAATGGCTTTCAA
AGCAGAAGGAGAATATACAGCATTTTCAGGCAGAAGAAGAAGCTAATCTTCTTCGACGTC
AAAGGCAGTATCTAGAGCTAGAATGTCGTCGCTTCAAAAGAAGAATGTTACTTGGGCGAC
ATAACTTGGAACAGGACCTTGTCAGGGAGGAGTTAAACAAAAGGCAGACTCAAAAGGACT
TGGAACATGCAATGCTATTGCGACAGCATGAATCAATGCAAGAACTGGAGTTTCGCCATC
TCAACACTATTCAGAAGATGCGCTGTGAGTTGATCAGACTGCAGCATCAAACTGAGCTCA
CTAACCAGCTAGAGTACAATAAGAGAAGGGAACGGGAACTGAGGCGAAAACATGTCATGG

Fig. 9R

AAGTTCGACAACAACCTAAGAGTCTGAAGTCTAAAGAACTCCAAATAAAAAGCAGTTTC
AGGATACCTGCAAAATTCAAACCAGACAGTACAAAGCATTAAGGAATCACCTACTGGAGA
CTACACCAAAGAATGAGCACAAAGCAATC

SEQ ID NO: 25 GEK2 HUMAN
CGAAGCCACAGCCCGAGCCCGAGCCCGAGCCCGAGCCGGCGCCACCGCGCCCCCGGCCAT
GGCTTTTGCCAATTTCCGCCGCATCCTGCGCCTGTCTACCTTCGAGAAGAGAAAGTCCCG
CGAATATGAGCACGTCCGCCGCGACCTGGACCCCAACGAGGTGTGGGAGATCGTGGGCGA
GCTGGGCGACGGCGCCTTCGGCAAGGTTTACAAGGCCAAGAATAAGGAGACGGGTGCTTT
GGCTGCGGCCAAAGTCATTGAAACCAAGAGTGAGGAGGAGCTGGAGGACTACATCGTGGA
GATTGAGATCCTGGCCACCTGCGACCACCCCTACATTGTGAAGCTCCTGGGAGCCTACTA
TCACGACGGGAAGCTGTGGATCATGATTGAGTTCTGTCCAGGGGGAGCCGTGGACGCCAT
CATGCTGGAGCTGGACAGAGGCCTCACGGAGCCCCAGATACAGGTGGTTTGCCGCCAGAT
GCTAGAAGCCCTCAACTTCCTGCACAGCAAGAGGATCATCCACCGAGATCTGAAAGCTGG
CAACGTGCTGATGACCCTCGAGGGAGACATCAGGCTGGCTGACTTTGGTGTGTCTGCCAA
GAATCTGAAGACTCTACAGAAACGAGATTCCTTCATCGGCACGCCTTACTGGATGGCCCC
CGAGGTGGTCATGTGTGAGACCATGAAAGACACGCCCTACGACTACAAAGCCGACATCTG
GTCCCTGGGCATCACGCTGATTGAGATGGCCCAGATCGAGCCGCCACACCACGAGCTCAA
CCCCATGCGGGTCCTGCTAAAGATCGCCAAGTCGGACCCTCCCACGCTGCTCACGCCCTC
CAAGTGGTCTGTAGAGTTCCGTGACTTCCTGAAGATAGCCCTGGATAAGAACCCAGAAAC
CCGACCCAGTGCCGCGCAGCTGCTGGAGCATCCCTTCGTCAGCAGCATCACCAGTAACAA
GGCTCTGCGGGAGCTGGTGGCTGAGGCCAAGGCCGAGGTGATGGAAGAGATCGAAGACGG
CCGGGATGAGGGGGAAGAGGAGGACGCCGTGGATGCCGCCTCCACCCTGGAGAACCATAC
TCAGAACTCCTCTGAGGTGAGTCCGCCAAGCCTCAATGCTGACAAGCCTCTCGAGGAGTC
ACCTTCCACCCCGCTGGCACCCAGCCAGTCTCAGGACAGTGTGAATGAGCCCTGCAGCCA
GCCCTCTGGGGACAGATCCCTCCAAACCACCAGTCCCCCAGTCGTGGCCCCTGGAAATGA
GAACGGCCTGGCAGTGCCTGTGCCCCTGCGGAAGTCCCGACCCGTGTCAATGGATGCCAG
AATTCAGGTAGCCCAGGAGAAGCAAGTTGCTGAGCAGGGTGGGGACCTCAGCCCAGCAGC
CAACAGATCTCAAAAGGCCAGCCAGAGCCGGCCCAACAGCAGCGCCCTGGAGACCTTGGG
TGGGGAGAAGCTGGCCAATGGCAGCCTGGAGCCACCTGCCCAGGCAGCTCCAGGGCCTTC
CAAGAGGGACTCGGACTGCAGCAGCCTCTGCACCTCTGAGAGCATGGACTATGGTACCAA
TCTCTCCACTGACCTGTCGCTGAACAAAGAGATGGGCTCTCTGTCCATCAAGGACCCGAA
ACTGTACAAAAAAACCCTCAAGCGGACACGCAAATTTGTGGTGGATGGTGTGGAGGTGAG
CATCACCACCTCCAAGATCATCAGCGAAGATGAGAAGAAGGATGAGGAGATGAGATTTCT
CAGGCGCCAGGAACTCCGAGAGCTTCGGCTGCTCCAGAAAGAAGAGCATCGGAACCAGAC
CCAGCTGAGTAACAAGCATGAGCTGCAGCTGGAGCAAATGCATAAACGTTTTGAACAGGA
AATCAACGCCAAGAAGAAGTTCTTTGACACGGAATTAGAGAACCTGGAGCGTCAGCAAAA
GCAGCAAGTGGAGAAGATGGAGCAAGACCATGCCGTGCGCCGCCGGGAGGAGGCCAGGCG

Fig. 9S

GATCCGCCTGGAGCAGGATCGGGACTACACCAGGTTCCAAGAGCAGCTCAAACTGATGAA
GAAAGAGGTGAAGAACGAGGTGGAGAAGCTCCCCGACAGCAGCGGAAGGAAAGCATGAA
GCAGAAGATGGAGGAGCACACGCAGAAAAAGCAGCTTCTTGACCGGGACTTTGTAGCCAA
GCAGAAGGAGGACCTGGAGCTGGCCATGAAGAGGCTCACCACCGACAACAGGCGGGAGAT
CTGTGACAAGGAGCGCGAGTGCCTCATGAAGAAGCAGGAGCTCCTTCGAGACCGGGAAGC
AGCCCTGTGGGAGATGGAAGAGCACCAGCTGCAGGAGAGGCACCAGCTGGTGAAGCAGCA
GCTCAAAGACCAGTACTTCCTCCAGCGGCACGAGCTGCTGCGCAAGCATGAGAAGGAGCG
GGAGCAGATGCAGCGCTACAACCAGCGCATGATAGAGCAGCTGAAGGTGCGGCAGCAACA
GGAAAAGGCGCGGCTGCCCAAGATCCAGAGGAGTGAGGGCAAGACGCGCATGGCCATGTA
CAAGAAGAGCCTCCACATCAACGGCGGGGGCAGCGCAGCTGAGCAGCGTGAGAAGATCAA
GCAGTTCTCCCAGCAGGAGGAGAAGAGGCAGAAGTCGGAGCGGCTGCAGCAACAGCAGAA
ACACGAGAACCAGATGCGGGACATGCTGGCGCAGTGCGAGAGCAACATGAGCGAGCTGCA
GCAGCTGCAGAATGAAAAGTGCCACCTCCTGGTAGAGCACGAAACCCAGAAACTGAAGGC
CCTGGATGAGAGCCATAACCAGAACCTGAAGGAAT

SEQ ID NO: 27 PAK4 HUMAN
CGTTCCTGGGCTTCCCGCTCCGCAGGCCTGCGGAGGACTGGCCCAGCAAGGTCCCAGGTC
TTCCCTCTCCTTAGCGCCTAAGAGAGAGGCCCAGTGCGGGTGAGGAGTCGCGAGGAAGAG
GCGGAAGGCGCCGGAAGGCACCATGTTCCGCAAGAAAAAGAAGAAACGCCCTGAGATCTC
AGCGCCACAGAACTTCCAGCACCGTGTCCACACCTCCTTCGACCCCAAAGAAGGCAAGTT
TGTGGGCCTCCCCCCACAATGGCAGAACATCCTGGACACACTGCGGCGCCCCAAGCCCGT
GGTGGACCCTTCGCGAATCACACGGGTGCAGCTCCAGCCCATGAAGACAGTGGTGCGGGG
CAGCGCGATGCCTGTGGATGGCTACATCTCGGGGCTGCTCAACGACATCCAGAAGTTGTC
AGTCATCAGCTCCAACACCCTGCGTGGCCGCAGCCCCACCAGCCGGCGGCGGGCACAGTC
CCTGGGGCTGCTGGGGGATGAGCACTGGGCCACCGACCCAGACATGTACCTCCAGAGCCC
CCAGTCTGAGCGCACTGACCCCCACGGCCTCTACCTCAGCTGCAACGGGGGCACACCAGC
AGGCCACAAGCAGATGCCGTGGCCCGAGCCACAGAGCCCACGGGTCCTGCCCAATGGGCT
GGCTGCAAAGGCACAGTCCCTGGGCCCCGCCGAGTTTCAGGGTGCCTCGCAGCGCTGTCT
GCAGCTGGGTGCCTGCCTGCAGAGCTCCCCACCAGGAGCCTCGCCCCCCACGGGCACCAA
TAGGCATGGAATGAAGGCTGCCAAGCATGGCTCTGAGGAGGCCCGGCCACAGTCCTGCCT
GGTGGGCTCAGCCACAGGCAGGCCAGGTGGGGAAGGCAGCCCTAGCCCTAAGACCCGGGA
GAGCAGCCTGAAGCGCAGGCTATTCCGAAGCATGTTCCTGTCCACTGCTGCCACAGCCCC
TCCAAGCAGCAGCAAGCCAGGCCCTCCACCACAGAGCAAGCCCAACTCCTCTTTCCGACC
GCCGCAGAAAGACAACCCCCCAAGCCTGGTGGCCAAGGCCCAGTCCTTGCCCTCGGACCA
GCCGGTGGGGACCTTCAGCCCTCTGACCACTTCGGATACCAGCAGCCCCCAGAAGTCCCT
CCGCACAGCCCCGGCCACAGGCCAGCTTCCAGGCCGGTCTTCCCCAGCGGGATCCCCCCG
CACCTGGCACGCCCAGATCAGCACCAGCAACCTGTACCTGCCCCAGGACCCCACGGTTGC
CAAGGGTGCCCTGGCTGGTGAGGACACAGGTGTTGTGACACATGAGCAGTTCAAGGCTGC

Fig. 9T

GCTCAGGATGGTGGTGGACCAGGGTGACCCCCGGCTGCTGCTGGACAGCTACGTGAAGAT
TGGCGAGGGCTCCACCGGCATCGTCTGCTTGGCCCGGGAGAAGCACTCGGGCCGCCAGGT
GGCCGTCAAGATGATGGACCTCAGGAAGCAGCAGCGCAGGGAGCTGCTCTTCAACGAGGT
GGTGATCATGCGGGACTACCAGCACTTCAACGTGGTGGAGATGTACAAGAGCTACCTGGT
GGGCGAGGAGCTGTGGGTGCTCATGGAGTTCCTGCAGGGAGGAGCCCTCACAGACATCGT
CTCCCAAGTCAGGCTGAATGAGGAGCAGATTGCCACTGTGTGTGAGGCTGTGCTGCAGGC
CCTGGCCTACCTGCATGCTCAGGGTGTCATCCACCGGGACATCAAGAGTGACTCCATCCT
GCTGACCCTCGATGGCAGGGTGAAGCTCTCGGACTTCGGATTCTGTGCTCAGATCAGCAA
AGACGTCCCTAAGAGGAAGTCCCTGGTGGGAACCCCCTACTGGATGGCTCCTGAAGTGAT
CTCCAGGTCTTTGTATGCCACTGAGGTGGATATCTGGTCTCTGGGCATCATGGTGATTGA
GATGGTAGATGGGGAGCCACCGTACTTCAGTGACTCCCCAGTGCAAGCCATGAAGAGGCT
CCGGGACAGCCCCCCACCCAAGCTGAAAAACTCTCACAAGGTCTCCCCAGTGCTGCGAGA
CTTCCTGGAGCGGATGCTGGTGCGGGACCCCCAAGAGAGAGCCACAGCCCAGGAGCTCCT
AGACCACCCCTTCCTGCTGCAGACAGGGCTACCTGAGTGCCTGGTGCCCCTGATCCAGCT
CTACCGAAAGCAGACCTCCACCTGCTGAGCCCACCCCAAGTATGCCTGCCACCTACGCCC
ACAGGCAGGGCACACTGGGCAGCCAGCCTGCCGGCAGGACTTGCCTGCCTCCTCCTCTCA
GTATTCTCTCCAAAGATTGAAATGTGAAGCCCCAGCCCCACCCTCTGCCCTTCAGCCTAC
TGGGCCAGGCCGGACCTGCCCCCTCAGTGTCTCTCCCTCCCGAGTCCCCAGATGGAGACC
CCTTTCTACAGGATGACCCCTTGATATTTGCACAGGGATATTTCTAAGAAACGCAGAGGC
CAGCGTTCCTGGCCTCTGCAGCCAACACAGTAGAAAAGGCTGCTGTGGTTTTTTAAAGGC
AGTTGTCCACTAGTGTCCTAGGCCACTGCAGAGGGCAGACTGCTGGTCTCCACAGATACC
TGCTGTTCTCAGCTCCAGCTTCAAACCTCGAGTCTCGAGAGGGCCACGGGGTGGTTTTTA
TGACCGGAATCCCGCTTCCTCCCTCACGTCTGATGTCCTGAAGGTGCAGTCCCACCTGTA
CAGCCCCTCCCCGCCAAGAACTGTGAATGGCCTGCTCCAGGCCATGGCTGGGGGCAGGGA
GTGAGGGGACAATTTCTGAGTGAAAGAGAAAGAATGGGGTCGGTGGTGAAGGTGCTCTCA
CTTTACAGAATGGAGAGAACATCGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTG
TGTGTGTGTGTGTGTGTGTGTGTGTGTGTAAGGGGAGGAAAGCCACCTTGACAGCCCAGGTC
CCTCCAGGTCACCCACAGCCAGTTTCAGGAAGGCTGCCCCTCTCTCCCACTAAGTTCTGG
CCTGAAGGGACCTGCTTTCTTGGCCTGGCTTCCACCTCTCCACTCCTGTGTCTACCTGGC
CAGTGGAGTGGTCCATGCTAAGTCTAACACTCCTGGGAGCTCAGGAGGCTTCTGAGCTTC
TCCTGTACTGTGCATCGTGAGGGCCAGAGACAGGAATGTAAGGATTGGCAACTGTGTTAC
CTTTCAAGTTTATCTCAATAACCAGGTCATCAGGGACCCATTGTTCTCTTCAGAACCCTA
TCTGGGAGAGAAGGCGAACCACCTCCGGGTTTCCATCATGTCAAGGTCACAGGCATCCAT
GTGTGCAAACCATCTGCCCCAGCTGCCTCCACAGACTGCTGTCTCCTTGTCCTCCTCGGC
CCTGCCCCACTTCAGGGCTGCTGTGAGATGGAATTCCAGGAAAGAACTTCAGGTGTCTGG
ACCCTTTCTATCTAGATAATATTTTTAGATTCTTCTGCTCCCTAGTGACCTACCTGGGGG
CAAAGAAATTGCAAGGACTTTTTTTTAAGGGTCAGAGTTTTCAAAACAAAAGCATCTTCC
CTAGAAATTTTTGTGAATTGTTTGCACTTGTGCCTGTTTTAAATTAAATTGAGTGTTCAA

Fig. 9U

AGCC

SEQ ID NO: 28 PAK5 HUMAN
GGCCAGTGGGGCGAAACTGGCAGCTGGCCGGCCCTTTAACACCTACCCGAGGGCTGACAC
GGACCACCCATCCCGGGGTGCCCAGGGGGAGCCTCATGACGTGGCCCCTAACGGGCCATC
AGCGGGGGGCCTGGCCATCCCCCAGTCCTCCTCCTCCTCCCGGCCTCCCACCCGAGC
CCGAGGTGCCCCCAGCCCTGGAGTGCTGGGACCCCACGCCTCAGAGCCCCAGCTGGCCCC
TCCAGCCTGCACCCCCGCCGCCCCTGCTGTTCCTGGGCCCCCTGGCCCCCGCTCACCACA
GCGGGAGCCACAGCGAGTATCCCATGAGCAGTTCCGGGCTGCCCTGCAGCTGGTGGTGGA
CCCAGGCGACCCCCGCTCCTACCTGGACAACTTCATCAAGATTGGCGAGGGCTCCACGGG
CATCGTGTGCATCGCCACCGTGCGCAGCTCGGGCAAGCTGGTGGCCGTCAAGAAGATGGA
CCTGCGCAAGCAGCAGAGGCGCGAGCTGCTCTTCAACGAGGTGGTAATCATGAGGGACTA
CCAGCACGAGAATGTGGTGGAGATGTACAACAGCTACCTGGTGGGGGACGAGCTCTGGGT
GGTCATGGAGTTCCTGGAAGGAGGCGCCCTCACCGACATCGTCACCCACACCAGGATGAA
CGAGGAGCAGATCGCGGCCGTGTGCCTTGCAGTGCTGCAGGCCCTGTCGGTGCTCCACGC
CCAGGGCGTCATCCACCGGGACATCAAGAGCGACTCGATCCTGCTGACCCATGATGGCAG
GGTGAAGCTGTCAGACTTTGGGTTCTGCGCCCAGGTGAGCAAGGAAGTGCCCCGAAGGAA
GTCGCTGGTCGGCACGCCCTACTGGATGGCCCCAGAGCTCATCTCCCGCCTTCCCTACGG
GCCAGAGGTAGACATCTGGTCGCTGGGGATAATGGTGATTGAGATGGTGGACGGAGAGCC
CCCCTACTTCAACGAGCCACCCCTCAAAGCCATGAAGATGATTCGGGACAACCTGCCACC
CCGACTGAAGAACCTGCACAAGGTGTCGCCATCCCTGAAGGGCTTCCTGGACCGCCTGCT
GGTGCGAGACCCTGCCCAGCGGGCCACGGCAGCCGAGCTGCTGAAGCACCCATTCCTGGC
CAAGGCAGGGCCGCCTGCCAGCATCGTGCCCCTCATGCGCCAGAACCGCACCAGATGAGG
CCCAGCGCCCTTCCCCTCAACCAAAGAGCCCCCCCGGGTCACCCCCGCCCCACTGAGGCC
AGTAGGGGGCCAGGCCTCCCACTCCTCCCAGCCCGGGAGATGCTCCGCGTGGCACCACCC
TCCTTGCTGGGGGTAGATGAGACCCTACTACTGAACTCCAGTTTTGATCTCGTGACTTTT
AGAAAAACACAGGGACTCGTGGGAGCAAGCGAGGCTCCCAGGACCCCCACCCTCTGGGAC
AGGCCCTCCCCCATGTTCTTCTGTCTCCAGGAAGGGCAGCGGCCCTCCCATCACTGGAAG
TCTGCAGTGGGGGTCGCTGGGGGTGGAGAGAACACTAAGAGGTGAACATGTATGAGTGTG
TGCACGCGTGTGAGTGTGCATGTGTGTGTGTGTGCAAAGGTCCAGCCACCCCGTCCTCCA
GCCCGCAAGGGGTGTCTGGCGCCTTGCCTGACACCCAGCCCCCTCTCCCCCTGAGCCATT
GTGGGGGTCGATCATGAATGTCCGAAGAGTGGCCTTTTCCCGTAGCCCTGCGCCCCCTTT
CTGTGGCTGGATGGGGAGACAGGTCAGGGCCCCCCACCCTCTCCAGCCCCTGCAGCAAAT
GACTACTGCACCTGGACAGCCTCCTCTTTTCTAGAAGTCTATTTATATTGTCATTTTATA
ACACTCTAGCCCCTGCCCTTATTGGGGGACAGATGGTCCCTGTCCTGCGGGGTGGCCCTG
GCAGAACCACTGCCTGAAGAACCAGGTTCCTGCCCGGTCAGCGCAGCCCCAGCCCGCCCA
CCCCTGCCTCGAGTTAGTTTTACAATTAAAACATTGTCTTGTTTTGTGAAAAAAAAAAAA
AAAAAAAAAA

Fig. 9V

>STLK5_h
MSSFLPEGGCYELLTVIGKGFEDLMTVNLARYKPTGEYVTVRRINLEACSNEMVTFLQGELHVSKLFNHPNIVPYRATFI
ADNELWVVTSFMAYGSAKDLICTHFMDGMNELAIAYILQGVLKALDYIHHMGYVHRSVKASHILISVDGKVYLSGLRSNL
SMISHGQRQRVVHDFPKYSVKVLPWLSPEVLQQNLQGYDAKSDIYSVGITACELANGHVPFKDMPATQMLLEKLNGTVPC
LLDTSTIPAEELTMSPSRSVANSGLSDSLTTSTPRPSNGDSPSHPYHRTFSPHFHHFVEQCLQRNPDARPSASTLLNHSF
FKQIKRRASEALPELLRPVTPITNFEGSQSQDHSGIFGLVTNLEELEVDDWEF

>STLK6_h
MSLLDCFCTSRTQVESLRPEKQSETSIHQYLVDEPTLSWSRPSTRASEVLCSTNVSHYELQVEIGRGFDNLTSVHLARHT
PTGTLVTIKITNLENCNEERLKALQKAVILSHFFRHPNITTYWTVFTVGSWLWVISPFMAYGSASQLLRTYFPEGMSETL
IRNILFGAVRGLNYLHQNGCIHRSIKASHILISGDGLVTLSGLSHLHSLVKHGQRHRAVYDFPQFSTSVQPWLSPELLRQ
DLHGYNVKSDIYSVGITACELASGQVPFQDMHRTQMLLQKLKGPPYSPLDISIFPQSESRMKNSQSGVDSGIGESVLVSS
GTHTVNSDRLHTPSSKTFSPAFFSLVQLCLQQDPEKRPSASSLLSHVFFKQMKEESQDSILSLLPPAYNKPSISLPPVLP
WTEPECDFPDEKDSYWEF

>STLK7_h
NRDDYELQEVIGSGATAVVQAAYCAPKKEKVAIKRINLEKCQTSMDELLKEIQAMSQCHHPNIVSYYTSFVVKDELWLVM
KLLSGGSVLDIIKHIVAKGEHKS

>ZC4_h
MAGPGGWRDREVTDLGHLPDPTGIFSLDKTIGLGTYGRIYLGLHEKTGAFTAVKVMNARKDEEEDLRTELNLLRKYSFHK
NIVSFYGAFFKLSPPGQRHQLWMVMELCAAGSVTDVVRMTSNQSLKEDWIAYICREILQGLAHLHAHRVIHRDIKGQNVL
LTHNAEVKLVDFGVSAQVSRTNGRRNSFIGTPYWMAPEVIDCDEDPRRSYDYRSDVWSVGITAIEMAEGAPPLCNLQPLE
ALFVILRESAPTVKSSGWSRKFHNFMEKCTIKNFLFRPTSANMLQHPFVRDIKNERHVVESLTRHLTGIIKKRQKKEQAR
EKKSKVSTLRQALAKRLSPKRFRAKSSWRPEKLELSDLEARRQRRQRRWEDIFNQHEEELRQVDKDKEDESSDNDEVFHS

Fig. 10A

IQAEVQIEPLKPYISNPKKIEVQERSPSVPNNQDHAHHVKFSSSVPQRSLLEQAQKPIDIRQRSSQNRQNWLAASGDSKH
KILAGKTQSYCLTIYISEVKKEEFQEGMNQKCQGAQVGLGPEGHCIWQLGESSSEEESPVTGRRSQSSPPYSTIDQKLLV
DIHVPDGFKVGKISPPVYLTNEWVGYNALSEIFRNDWLTPAPVIQPPEEDGDYVELYDASADTDGDDDDESNDTFEDTYD
HANGNDDLDNQVDQANDVCKDHDDDNNKFVDDVNNNYYEAPSCPRASYGRDGSCKQDGYDGSRGKEEAYRGYGSHTANRS
HGGSAASEDNAAIGDQEEHAANIGSERRGSEGDGGKGVVRTSEESGALGLNGEENCSETDGPGLKRPASQDFEYLQEEPG
GGNEASNAIDSGAAPSAPDHESDNKDISESSTQSDFSANHSSPSKGSGMSADANFASAILYAGFVEVPEESPKQPSEVNV
NPLYVSPACKKPLIHMYEKEFTSEICCGSLWGVNLLLGTRSNLYLMDRSGKADITKLIRRRPFRQIQVLEPLNLLITISG
HKNRLRVYHLTWLRNKILNNDPESKRRQEEMLKTEEACKAIDKLTGCEHFSVLQHEETTYIAIALKSSIHLYAWAPKSFD
ESTAIKVFPTLDHKPVTVDLAIGSEKRLKIFFSSADGYHLIDAESEVMSDVTLPKNPLEIIIPQNIIILPDCLGIGMMLT
FNAEALSVEANEQLFKKILEMWKDIPSSIAFECTQRTTGWGQKAIEVRSLQSRVLESELKRRSIKKLRFLCTRGDKLFFT
STLRNHHSRVYFMTLGKLEELQSNYDV

>PAK5_h
MFGKRKKRVEISAPSNFEHRVHTGFDQHEQKFTGLPRQWQSLIEESARRPKPLVDPACITSIQPGAPKTIVRGSKGAKDG
ALTLLLDEFENMSVTRSNSLRRDSPPPPARARQENGMPEEPATTARGGPGKAGSRGRFAGHSEAGGGSGDRRRAGPEKRP
KSSREGSGGPQESSRDKRPLSGPDVGTPQPAGLASGAKLAAGRPFNTYPRADTDHPSRGAQGEPHDVAPNGPSAGGLAIP
QSSSSSSRPPTRARGAPSPGVLGPHASEPQLAPPACTPAAPAVPGPPGPRSPQREPQRVSHEQFRAALQLVVDPGDPRSY
LDNFIKIGEGSTGIVCIATVRSSGKLVAVKKMDLRKQQRRELLFNEVVIMRDYQHENVVEMYNSYLVGDELWVVMEFLEG
GALTDIVTHTRMNEEQIAAVCLAVLQALSVLHAQGVIHRDIKSDSILLTHDGRVKLSDFGFCAQVSKEVPRRKSLVGTPY
WMAPELISRLPYGPEVDIWSLGIMVIEMVDGEPPYFNEPPLKAMKMIRDNLPPRLKNLHKVSPSLKGFLDRLLVRDPAQR
ATAAELLKHPFLAKAGPPASIVPLMRQNRTR

>GEK2_h
MAFANFRRILRLSTFEKRKSREYEHVRRDLDPNEVWEIVGELGDGAFGKVYKAKNKETGALAAAKVIETKSEEELEDYIV
EIEILATCDHPYIVKLLGAYYHDGKLWIMIEFCPGGAVDAIMLELDRGLTEPQIQVVCRQMLEALNFLHSKRIIHRDLKA

Fig. 10B

```
GNVLMTLEGDIRLADFGVSAKNLKTLQKRDSFIGTPYWMAPEVVMCETMKDTPYDYKADIWSLGITLIEMAQIEPPHHEL
NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLEHPFVSSITSNKALRELVAEAKAEVMEEIED
GRDEGEEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEESPSTPLAPSQSQDSVNEPCSQPSGDRSLQTTSPPVVAPGN
ENGLAVPVPLRKSRPVSMDARIQVAQEKQVAEQGGDLSPAANRSQKASQSRPNSSALETLGGEKLANGSLEPPAQAAPGP
SKRDSDCSSLCTSESMDYGTNLSTDLSLNKEMGSLSIKDPKLYKKTLKRTRKFVVDGVEVSITTSKIISEDEKKDEEMRF
LRRQELRELRLLQKEEHRNQTQLSNKHELQLEQMHKRFEQEINAKKKFFDTELENLERQQKQQVEKMEQDHAVRRREEAR
RIRLEQDRDYTRFQEQLKLMKKEVKNEVEKLPRQQRKESMKQKMEEHTQKKQLLDRDFVAKQKEDLELAMKRLTTDNRRE
ICDKERECLMKKQELLRDREAALWEMEEHQLQERHQLVKQQLKDQYFLQRHELLRKHEKEREQMQRYNQRMIEQLKVRQQ
QEKARLPKIQRSEGKTRMAMYKKSLHINGGGSAAEQREKIKQFSQQEEKRQKSERLQQQQKHENQMRDMLAQCESNMSEL
QQLQNEKCHLLVEHETQKLKALDESHNQNLKEWRDKLRPRKKALEEDLNQKKREQEMFFKLSEEAECPNPSTPSKAAKFF
PYSSGDAS
```

Fig. 10C

>STLK5_h
GGCCAAGACGGTCGGGGCTGCTTGCTAACTCCAGGAACAGGTTTAAGTTTTTGAAACTGAAGTAGGTCTACACAGTAGGA
ACTCATGTCATTTCTTGTAAGTAAACCAGAGCGAATCAGGCGGTGGGTCTCGGAAAAGTTCATTGTTGAGGGCTTAAGAG
ATTTGGAACTATTTGGAGACCAATGATGCGAGCTCAGAGTCAATAGCATCCTTCTCTAAACAGGAGGTCATGAGTAGCTT
TCTGCCAGAGGGAGGGTGTTACGAGCTGCTCACTGTGATAGGCAAAGGATTTGAGGACCTGATGACTGTGAATCTAGCAA
GGTACAAACCAACAGGAGAGTACGTGACTGTACGGAGGATTAACCTAGAAGCTTGTTCCAATGAGATGGTAACATTCTTG
CAGGGCGAGCTGCATGTCTCCAAACTCTTCAACCATCCCAATATCGTGCCATATCGAGCCACTTTTATTGCAGACAATGA
GCTGTGGGTTGTCACATCATTCATGGCATACGGTTCTGCAAAAGATCTCATCTGTACACACTTCATGGATGGCATGAATG
AGCTGGCGATTGCTTACATCCTGCAGGGGGTGCTGAAGGCCCTCGACTACATCCACCACATGGGATATGTACACAGGAGT
GTCAAAGCCAGCCACATCCTGATCTCTGTGGATGGGAAGGTCTACCTGTCTGGTTTGCGCAGCAACCTCAGCATGATAAG
CCATGGGCAGCGGCAGCGAGTGGTCCACGATTTTCCCAAGTACAGTGTCAAGGTTCTGCCGTGGCTCAGCCCCGAGGTCC
TCCAGCAGAATCTCCAGGGTTATGATGCCAAGTCTGACATCTACAGTGTGGGAATCACAGCCTGTGAACTGGCCAACGGC
CATGTCCCCTTTAAGGATATGCCTGCCACCCAGATGCTGCTAGAGAAACTGAACGGCACAGTGCCCTGCCTGTTGGATAC
CAGCACCATCCCCGCTGAGGAGCTGACCATGAGCCCTTCGCGCTCAGTGGCCAACTCTGGCCTGAGTGACAGCCTGACCA
CCAGCACCCCCCGGCCCTCCAACGGTGACTCGCCCTCCCACCCCTACCACCGAACCTTCTCCCCCCACTTCCACCACTTT
GTGGAGCAGTGCCTTCAGCGCAACCCGGATGCCAGGCCCAGTGCCAGCACCCTCCTGAACCACTCTTTCTTCAAGCAGAT
CAAGCGACGTGCCTCAGAGGCTTTGCCCGAATTGCTTCGTCCTGTCACCCCCATCACCAATTTTGAGGGCAGCCAGTCTC
AGGACCACAGTGGAATCTTTGGCCTGGTAACAAACCTGGAAGAGCTGGAGGTGGACGATTGGGAGTTCTGAGCCTCTGCA
AACTGTGCGCATTCTCCAGCCAGGGATGCAGAGGCCACCCAGAGGCCCTTCCTGAGGGCCGGCCACATTCCCGCCCTCCT
GGGCAGATTGGGTAGAAAGGACATTCTTCCAGGAAAGTTGACTGCTGACTGATTGGGAAAGAAAATCCTGGAGAGATACT
TCACTGCTCCAAGGCTTTTGAGACACAAGGGAATCTCAACAACCAGGGATCAGGAGGGTCCAAAGCCGACATTCCCAGTC
CTGTGAGCTCAGGTGACCTCCTCCGCAGAAGAGAGATGCTGCTCTGGCCCTGGGAGCTGAATTCCAAGCCCAGGGTTTGG
CTCCTTAAACCCGAGGACCGCCACCTCTTCCCAGTGCTTGCGACCAGCCTCATTCTATTTAACTTTGCTCTCAGATGCCT
CAGATGCTATAGGTCAGTGAAAGGGCAAGTAGTAAGCTGCCTGCCTCCCTTCCCTCAGACCTCTCCCTCATAATTCCAGA
GAAGGGCATTTCTGTCTTTTTAAGCACAGACTAAGGCTGGAACAGTCCATCCTTATCCCTCTTCTGGCTTGGGCCCTGAC

Fig. 11A

ACCTAAGTCTTTCCCACGGTTTATGTGTGTGCCTCATTCCTTTCCCACCAAGAATCCATCTTAGCGCCTCCTGCCAGCTG
CCCTGGTGCTTTCTCCAAGGGCCATCAGTGTCTTGCCTAGCTTGAGGGCTTAAGTCCTTATGCTGTGTTAGTTTCGTTGT
CAGAACAAATTAAAATTTTCAGAGACGCTG

>STLK6_h
AAGGAAGATAAAACAAAAGCCTTCTTTGGAATAGATGGATTTTTGTCACTTTCTGTGTGAACTAAAGTGATTCAATGTCT
CTTTTGGATTGCTTCTGCACTTCAAGAACACAAGTTGAATCACTCAGACCTGAAAAACAGTCTGAAACCAGTATCCATCA
ATACTTGGTTGATGAGCCAACCCTTTCCTGGTCACGTCCATCCACTAGAGCCAGTGAAGTACTATGTTCCACCAACGTTT
CTCACTATGAGCTCCAAGTAGAAATAGGAAGAGGATTTGACAACTTGACTTCTGTCCATCTTGCACGGCATACTCCCACG
GGAACACTGGTAACTATAAAAATTACAAATCTGGAAAACTGCAATGAAGAACGCCTGAAAGCTTTACAGAAAGCCGTGAT
TCTATCCCACTTTTTCCGGCATCCCAATATTACAACTTATTGGACAGTTTTCACTGTTGGCAGCTGGCTTTGGGTTATTT
CTCCATTTATGGCCTATGGTTCAGCAAGTCAACTCTTGAGGACCTATTTTCCTGAAGGAATGAGTGAAACTTTAATAAGA
AACATTCTCTTTGGAGCCGTGAGAGGGTTGAACTATCTGCACCAAAATGGCTGTATTCACAGGAGTATTAAAGCCAGCCA
TATCCTCATTTCTGGTGATGGCCTAGTGACCCTCTCTGGCCTTTCCCATCTGCATAGTTTGGTTAAGCATGGACAGAGGC
ATAGGGCTGTGTATGATTTCCCACAGTTCAGCACATCAGTGCAGCCGTGGCTGAGTCCAGAACTACTGAGACAGGATTTA
CATGGGTATAATGTGAAGTCAGATATTTACAGTGTTGGGATTACAGCATGTGAATTAGCCAGTGGGCAGGTGCCTTTCCA
GGACATGCATAGAACTCAGATGCTGTTACAGAAACTGAAAGGTCCTCCTTATAGCCCATTGGATATCAGTATTTTCCCTC
AATCAGAATCCAGAATGAAAAATTCCCAGTCAGGTGTAGACTCTGGGATTGGAGAAAGTGTGCTTGTCTCCAGTGGAACT
CACACAGTAAATAGTGACCGATTACACACACCATCCTCAAAAACTTTCTCTCCTGCCTTCTTTAGCTTGGTACAGCTCTG
TTTGCAACAAGATCCTGAGAAAAGGCCATCAGCAAGCAGTTTATTGTCCCATGTTTTCTTCAAACAGATGAAAGAAGAAA
GCCAGGATTCAATACTTTCACTGTTGCCTCCTGCTTATAACAAGCCATCAATATCATTGCCTCCAGTGTTACCTTGGACT
GAGCCAGAATGTGATTTTCCTGATGAAAAAGACTCATACTGGGAATTCTAGGGCTGCCAAATCATTTTATGTCCTATATA
CTTGACACTTTCTCCTTGCTGCTTTTTCTTCTGTATTTCTAGGTACAAATACCAGAATTATACTTGAAAATACAGTTGGT
GCACTGGAGAATCTATTATTTAAAACCACTCTGTTCAAAGGGGCACCAGTTTGTAGTCCCTCTGTTTCGCACAGAGTACT
ATGACAAGGAAACATCAGAATTACTAATCTAGCTAGTGTCATTTATTCTGGAATTTTTTTCTAAGCTGTGACTAACTCTT

Fig. 11B

TTTATCTCTCAATATAATTTTTGAGCCAGTTAATTTTTTTCAGTATTTTGCTGTCCCTTGGGAATGGGCCCTCAGAGGAC
AGTGCTTCCAAGTACATCTTCTCCCAGATTCTCTGGCCTTTTTAATGAGCTATTGTTAAACCAACAGGCTAGTTTATCTT
ACATCAGACCCTTTTCTGGTAGAGGGAAAATGTTTGTGCTTTCCCTTTTTCTTCTGTTAATACTTATGGTAACACCTAAC
TGAGCCTCACTCACATTAAATGATTCACTTGAAATATATACAGAAATTGTAATTTGCTTTTTTTTAAAAAAGGGGGCTAA
AGTAACACTTTCCTACTTATGTAAATTATAGATCCTAAATTCACGCACCCCGTGGGAGCTCAATAAAGATTTACTGAATT
G

>STLK7_h
TCAACAGGGACGATTACGAGCTGCAGGAGGTGATCGGGAGTGGAGCAACTGCTGTAGTCCAAGCAGCTTATTGTGCCCCT
AAAAAGGAGAAAGTGGCAATCAAACGGATAAACCTTGAGAAATGTCAAACTAGCATGGATGAACTCCTGAAAGAAATTCA
AGCCATGAGTCAATGCCATCATCCTAATATTGTATCTTACTACACATCTTTTGTGGTAAAAGATGAGCTGTGGCTTGTCA
TGAAGCTGCTAAGTGGAGGTTCTGTTCTGGATATTATTAAGCACATTGTGGCAAAAGGGGAACACAAAAGT

>ZC4_h
ATGGCGGGACCTGGGGGCTGGAGGGACAGGGAGGTCACGGATCTGGGCCACCTGCCGGATCCAACTGGAATATTCTCACT
AGATAAAACCATTGGCCTTGGTACTTATGGCAGAATCTATTTGGGACTTCATGAGAAGACTGGTGCATTTACAGCTGTTA
AAGTGATGAACGCTCGTAAGGATGAGGAAGAGGATCTCAGGACTGAACTCAACCTTCTGAGGAAGTACTCTTTCCACAAA
AACATTGTGTCCTTCTATGGAGCATTTTTCAAGCTGAGTCCCCCTGGTCAGCGGCACCAACTTTGGATGGTGATGGAGTT
ATGTGCAGCAGGTTCGGTCACTGATGTAGTGAGAATGACCAGTAATCAGAGTTTAAAAGAAGATTGGATTGCTTATATCT
GCCGAGAAATCCTTCAGGGCTTAGCTCACCTTCACGCACACCGAGTAATTCACCGGGACATCAAAGGTCAGAATGTGCTG
CTGACTCATAATGCTGAAGTAAAACTGGTTGATTTTGGAGTGAGTGCCCAGGTGAGCAGAACTAATGGAAGAAGGAATAG
TTTCATTGGGACACCATACTGGATGGCACCTGAGGTGATTGACTGTGATGAGGACCCAAGACGCTCCTATGATTACAGAA
GTGATGTGTGGTCTGTGGGAATTACTGCCATTGAAATGGCTGAAGGAGCCCCTCCTCTGTGTAACCTTCAACCCTTGGAA
GCTCTCTTCGTTATTTTGCGGGAATCTGCTCCCACAGTCAAATCCAGCGGATGGTCCCGTAAGTTCCACAATTTCATGGA
AAAGTGTACGATAAAAAATTTCCTGTTTCGTCCTACTTCTGCAAACATGCTTCAACACCCATTTGTTCGGGATATAAAAA

Fig. 11C

ATGAACGACATGTTGTTGAGTCATTAACAAGGCATCTTACTGGAATCATTAAAAAAAGACAGAAAAAAGAACAGGCACGG
GAGAAAAAATCAAAAGTTTCTACTCTGAGGCAAGCACTGGCAAAAAGACTATCACCAAAGAGGTTCAGGGCAAAGTCATC
ATGGAGACCTGAAAAGCTTGAACTCTCGGATTTAGAAGCCCGCAGGCAAAGGCGCCAACGCAGATGGGAAGATATCTTTA
ATCAGCATGAGGAAGAATTGAGACAAGTTGATAAAGACAAAGAAGATGAATCATCAGACAATGATGAAGTATTTCATTCG
ATTCAGGCTGAAGTCCAGATAGAGCCATTGAAGCCATACATTTCAAATCCTAAAAAAATTGAGGTTCAAGAGAGATCTCC
TTCTGTGCCTAACAACCAGGATCATGCACATCATGTCAAGTTCTCTTCAAGCGTTCCTCAGCGGTCTCTTTTGGAACAAG
CTCAGAAGCCCATTGACATCAGACAAAGGAGTTCGCAAAATCGTCAAAATTGGCTGGCAGCATCAGGTGATTCAAAGCAC
AAAATTTTAGCAGGCAAAACACAGAGCTACTGTTTAACAATTTATATTTCAGAAGTCAAGAAAGAAGAATTTCAAGAAGG
AATGAATCAAAAGTGTCAGGGAGCCCAAGTAGGATTAGGACCTGAAGGCCATTGTATTTGGCAATTGGGTGAATCTTCTT
CTGAGGAAGAAAGTCCTGTGACTGGAAGGAGGTCTCAGTCATCACCACCTTATTCTACTATTGATCAGAAGTTGCTGGTT
GACATCCATGTTCCAGATGGATTTAAAGTAGGAAAAATATCACCCCCTGTATACTTGACAAACGAATGGGTAGGCTATAA
TGCACTCTCTGAAATCTTCCGGAATGATTGGTTAACTCCGGCACCTGTCATTCAGCCACCTGAAGAGGATGGTGATTATG
TTGAACTCTATGATGCCAGTGCTGATACTGATGGTGATGATGATGATGAGTCTAATGATACTTTTGAAGATACCTATGAT
CATGCCAATGGCAATGATGACTTGGATAACCAGGTTGATCAGGCTAATGATGTTTGTAAAGACCATGATGATGACAACAA
TAAGTTTGTTGATGATGTAAATAATAATTATTATGAGGCGCCTAGTTGTCCAAGGGCAAGCTATGGCAGAGATGGAAGCT
GCAAGCAAGATGGTTATGATGGAAGTCGTGGAAAAGAGGAAGCCTACAGAGGCTATGGAAGCCATACAGCCAATAGAAGC
CATGGAGGAAGTGCAGCCAGTGAGGACAATGCAGCCATTGGAGATCAGGAAGAACATGCAGCCAATATAGGCAGTGAAAG
AAGAGGCAGTGAGGGTGATGGAGGTAAGGGAGTCGTTCGAACCAGTGAAGAGAGTGGAGCCCTTGGACTCAATGGAGAAG
AAAATTGCTCAGAGACAGATGGTCCAGGATTGAAGAGACCTGCGTCTCAGGACTTTGAATATCTACAGGAGGAGCCAGGT
GGTGGAAATGAGGCCTCAAATGCCATTGACTCAGGTGCTGCACCGTCAGCACCTGATCATGAGAGTGACAATAAGGACAT
ATCAGAATCATCAACACAATCAGATTTTTCTGCCAATCACTCATCTCCTTCCAAAGGTTCTGGGATGTCTGCTGATGCTA
ACTTTGCCAGTGCCATCTTATACGCTGGATTCGTAGAAGTACCTGAGGAATCACCTAAGCAACCCTCTGAAGTCAATGTT
AACCCACTCTATGTCTCTCCTGCATGTAAAAAACCACTAATCCACATGTATGAAAAGGAGTTCACTTCTGAGATCTGCTG
TGGTTCTTTGTGGGGAGTCAATTTGCTGTTGGGAACCCGATCTAATCTATATCTGATGGACAGAAGTGGAAAGGCTGACA
TTACTAAACTTATAAGGCGAAGACCATTCCGCCAGATTCAAGTCTTAGAGCCACTCAATTTGCTGATTACCATCTCAGGT

Fig. 11D

CATAAGAACAGACTTCGGGTGTATCATCTGACCTGGTTGAGGAACAAGATTTTGAATAATGATCCAGAAAGTAAAAGAAG
GCAAGAAGAAATGCTGAAGACAGAGGAAGCCTGCAAAGCTATTGATAAGTTAACAGGCTGTGAACACTTCAGTGTCCTCC
AACATGAAGAAACAACATATATTGCAATTGCTTTGAAATCATCAATTCACCTTTATGCATGGGCACCAAAGTCCTTTGAT
GAAAGCACTGCTATTAAAGTATTTCCAACACTTGATCATAAGCCAGTGACAGTTGACCTGGCTATTGGTTCTGAAAAAAG
ACTAAAGATTTTCTTCAGCTCAGCAGATGGATATCACCTCATCGATGCAGAATCTGAGGTTATGTCTGATGTGACCCTGC
CAAAGAATCCCCTGGAAATCATTATACCACAGAATATCATCATTTTACCTGATTGCTTGGGAATTGGCATGATGCTCACC
TTCAATGCTGAAGCCCTCTCTGTGGAAGCAAATGAACAACTCTTCAAGAAGATCCTTGAAATGTGGAAAGACATACCATC
TTCTATAGCTTTTGAATGTACACAGCGAACCACAGGATGGGGCCAAAAGGCCATTGAAGTGCGCTCTTTGCAATCCAGGG
TTCTGGAAAGTGAGCTGAAGCGCAGGTCAATTAAGAAGCTGAGATTCCTGTGCACCCGGGGTGACAAGCTGTTCTTTACC
TCTACCCTGCGCAATCACCACAGCCGGGTTTACTTCATGACACTTGGAAAACTTGAAGAGCTCCAAAGCAATTATGATGT
CTAA

>PAK5_h
CGGGAGTGTCCGCGGTGGTGGCGGTGCAAGAGAGCTGAAGGAGGCGCGAGGGCGCGGAGTTCCAGGCCGAGCAGTTAGGC
CGCGAGCGACTGCGGCGCCGAGCCGATGAGTAACCCGAAGCCCCTAGAGGAGTGGTCACCTGCCTGAGGGCACTTCTGTC
CCACCAGCATCAGACCAGGCCGCACCGAGTCCCCGGCACCATGTTTGGGAAGAGGAAGAAGCGGGTGGAGATCTCCGCGC
CGTCCAACTTCGAGCACCGCGTGCACACGGGCTTCGACCAGCACGAGCAGAAGTTCACGGGGCTGCCCCGCCAGTGGCAG
AGCCTGATCGAGGAGTCGGCTCGCCGGCCCAAGCCCCTCGTCGACCCCGCCTGCATCACCTCCATCCAGCCCGGGGCCCC
CAAGACCATCGTGCGGGGCAGCAAAGGTGCCAAAGATGGGGCCCTCACGCTGCTGCTGGACGAGTTTGAGAACATGTCGG
TGACACGCTCCAACTCCCTGCGGAGAGACAGCCCGCCGCCGCCCGCCCGTGCCCGCCAGGAAAATGGGATGCCAGAGGAG
CCGGCCACCACGGCCAGAGGGGGCCCAGGGAAGGCAGGCAGCCGAGGCCGGTTCGCCGGTCACAGCGAGGCGGGTGGCGG
CAGTGGTGACAGGCGACGGGCGGGGCCAGAGAAGAGGCCCAAGTCTTCCAGGGAGGGCTCAGGGGGTCCCCAGGAGTCCT
CCCGGGACAAACGCCCCCTCTCCGGGCCTGATGTCGGCACCCCCCAGCCTGCTGGTCTGGCCAGTGGGGCGAAACTGGCA
GCTGGCCGGCCCTTTAACACCTACCCGAGGGCTGACACGGACCACCCATCCCGGGGTGCCCAGGGGGAGCCTCATGACGT
GGCCCCTAACGGGCCATCAGCGGGGGGCCTGGCCATCCCCAGTCCTCCTCCTCCTCCCGGCCTCCCACCCGAGCCC

Fig. 11E

GAGGTGCCCCCAGCCCTGGAGTGCTGGGACCCCACGCCTCAGAGCCCCAGCTGGCCCCTCCAGCCTGCACCCCCGCCGCC
CCTGCTGTTCCTGGGCCCCCTGGCCCCCGCTCACCACAGCGGGAGCCACAGCGAGTATCCCATGAGCAGTTCCGGGCTGC
CCTGCAGCTGGTGGTGGACCCAGGCGACCCCCGCTCCTACCTGGACAACTTCATCAAGATTGGCGAGGGCTCCACGGGCA
TCGTGTGCATCGCCACCGTGCGCAGCTCGGGCAAGCTGGTGGCCGTCAAGAAGATGGACCTGCGCAAGCAGCAGAGGCGC
GAGCTGCTCTTCAACGAGGTGGTAATCATGAGGGACTACCAGCACGAGAATGTGGTGGAGATGTACAACAGCTACCTGGT
GGGGGACGAGCTCTGGGTGGTCATGGAGTTCCTGGAAGGAGGCGCCCTCACCGACATCGTCACCCACACCAGGATGAACG
AGGAGCAGATCGCGGCCGTGTGCCTTGCAGTGCTGCAGGCCCTGTCGGTGCTCCACGCCCAGGGCGTCATCCACCGGGAC
ATCAAGAGCGACTCGATCCTGCTGACCCATGATGGCAGGGTGAAGCTGTCAGACTTTGGGTTCTGCGCCCAGGTGAGCAA
GGAAGTGCCCCGAAGGAAGTCGCTGGTCGGCACGCCCTACTGGATGGCCCCAGAGCTCATCTCCCGCCTTCCCTACGGGC
CAGAGGTAGACATCTGGTCGCTGGGGATAATGGTGATTGAGATGGTGGACGGAGAGCCCCCCTACTTCAACGAGCCACCC
CTCAAAGCCATGAAGATGATTCGGGACAACCTGCCACCCCGACTGAAGAACCTGCACAAGGTGTCGCCATCCCTGAAGGG
CTTCCTGGACCGCCTGCTGGTGCGAGACCCTGCCCAGCGGGCCACGGCAGCCGAGCTGCTGAAGCACCCATTCCTGGCCA
AGGCAGGGCCGCCTGCCAGCATCGTGCCCCTCATGCGCCAGAACCGCACCAGATGAGGCCCAGCGCCCTTCCCCTCAACC
AAAGAGCCCCCCGGGTCACCCCCGCCCCACTGAGGCCAGTAGGGGGCCAGGCCTCCCACTCCTCCCAGCCCGGGAGATG
CTCCGCGTGGCACCACCCTCCTTGCTGGGGGTAGATGAGACCCTACTACTGAACTCCAGTTTTGATCTCGTGACTTTTAG
AAAAACACAGGGACTCGTGGGAGCAAGCGAGGCTCCCAGGACCCCCACCCTCTGGGACAGGCCCTCCCCCATGTTCTTCT
GTCTCCAGGAAGGGCAGCGGCCCTCCCATCACTGGAAGTCTGCAGTGGGGGTCGCTGGGGGTGGAGAGAACACTAAGAGG
TGAACATGTATGAGTGTGTGCACGCGTGTGAGTGTGCATGTGTGTGTGTGTGCAAAGGTCCAGCCACCCCGTCCTCCAGC
CCGCAAGGGGTGTCTGGCGCCTTGCCTGACACCCAGCCCCCTCTCCCCCTGAGCCATTGTGGGGGTCGATCATGAATGTC
CGAAGAGTGGCCTTTTCCCGTAGCCCTGCGCCCCCTTTCTGTGGCTGGATGGGGAGACAGGTCAGGGCCCCCCACCCTCT
CCAGCCCCTGCAGCAAATGACTACTGCACCTGGACAGCCTCCTCTTTTCTAGAAGTCTATTTATATTGTCATTTTATAAC
ACTCTAGCCCCTGCCCTTATTGGGGGACAGATGGTCCCTGTCCTGCGGGGTGGCCCTGGCAGAACCACTGCCTGAAGAAC
CAGGTTCCTGCCCGGTCAGCGCAGCCCCAGCCCGCCCACCCCTGCCTCGAGTTAGTTTTACAATTAAAACATTGTCTTGT
TTTGTG

Fig. 11F

>GEK2_h
CGAAGCCACAGCCCGAGCCCGAGCCCGAGCCCGAGCCGGCGCCACCGCGCCCCCGGCCATGGCTTTTGCCAATTTCCGCC
GCATCCTGCGCCTGTCTACCTTCGAGAAGAGAAAGTCCCGCGAATATGAGCACGTCCGCCGCGACCTGGACCCCAACGAG
GTGTGGGAGATCGTGGGCGAGCTGGGCGACGGCGCCTTCGGCAAGGTTTACAAGGCCAAGAATAAGGAGACGGGTGCTTT
GGCTGCGGCCAAAGTCATTGAAACCAAGAGTGAGGAGGAGCTGGAGGACTACATCGTGGAGATTGAGATCCTGGCCACCT
GCGACCACCCCTACATTGTGAAGCTCCTGGGAGCCTACTATCACGACGGGAAGCTGTGGATCATGATTGAGTTCTGTCCA
GGGGGAGCCGTGGACGCCATCATGCTGGAGCTGGACAGAGGCCTCACGGAGCCCCAGATACAGGTGGTTTGCCGCCAGAT
GCTAGAAGCCCTCAACTTCCTGCACAGCAAGAGGATCATCCACCGAGATCTGAAAGCTGGCAACGTGCTGATGACCCTCG
AGGGAGACATCAGGCTGGCTGACTTTGGTGTGTCTGCCAAGAATCTGAAGACTCTACAGAAACGAGATTCCTTCATCGGC
ACGCCTTACTGGATGGCCCCCGAGGTGGTCATGTGTGAGACCATGAAAGACACGCCCTACGACTACAAAGCCGACATCTG
GTCCCTGGGCATCACGCTGATTGAGATGGCCCAGATCGAGCCGCCACACCACGAGCTCAACCCCATGCGGGTCCTGCTAA
AGATCGCCAAGTCGGACCCTCCCACGCTGCTCACGCCCTCCAAGTGGTCTGTAGAGTTCCGTGACTTCCTGAAGATAGCC
CTGGATAAGAACCCAGAAACCCGACCCAGTGCCGCGCAGCTGCTGGAGCATCCCTTCGTCAGCAGCATCACCAGTAACAA
GGCTCTGCGGGAGCTGGTGGCTGAGGCCAAGGCCGAGGTGATGGAAGAGATCGAAGACGGCCGGGATGAGGGGGAAGAGG
AGGACGCCGTGGATGCCGCCTCCACCCTGGAGAACCATACTCAGAACTCCTCTGAGGTGAGTCCGCCAAGCCTCAATGCT
GACAAGCCTCTCGAGGAGTCACCTTCCACCCCGCTGGCACCCAGCCAGTCTCAGGACAGTGTGAATGAGCCCTGCAGCCA
GCCCTCTGGGGACAGATCCCTCCAAACCACCAGTCCCCCAGTCGTGGCCCCTGGAAATGAGAACGGCCTGGCAGTGCCTG
TGCCCCTGCGGAAGTCCCGACCCGTGTCAATGGATGCCAGAATTCAGGTAGCCCAGGAGAAGCAAGTTGCTGAGCAGGGT
GGGGACCTCAGCCCAGCAGCCAACAGATCTCAAAAGGCCAGCCAGAGCCGGCCCAACAGCAGCGCCCTGGAGACCTTGGG
TGGGGAGAAGCTGGCCAATGGCAGCCTGGAGCCACCTGCCCAGGCAGCTCCAGGGCCTTCCAAGAGGGACTCGGACTGCA
GCAGCCTCTGCACCTCTGAGAGCATGGACTATGGTACCAATCTCTCCACTGACCTGTCGCTGAACAAAGAGATGGGCTCT
CTGTCCATCAAGGACCCGAAACTGTACAAAAAAACCCTCAAGCGGACACGCAAATTTGTGGTGGATGGTGTGGAGGTGAG
CATCACCACCTCCAAGATCATCAGCGAAGATGAGAAGAAGGATGAGGAGATGAGATTTCTCAGGCGCCAGGAACTCCGAG
AGCTTCGGCTGCTCCAGAAAGAAGAGCATCGGAACCAGACCCAGCTGAGTAACAAGCATGAGCTGCAGCTGGAGCAAATG
CATAAACGTTTTGAACAGGAAATCAACGCCAAGAAGAAGTTCTTTGACACGGAATTAGAGAACCTGGAGCGTCAGCAAAA

Fig. 11G

GCAGCAAGTGGAGAAGATGGAGCAAGACCATGCCGTGCGCCGCCGGGAGGAGGCCAGGCGGATCCGCCTGGAGCAGGATC
GGGACTACACCAGGTTCCAAGAGCAGCTCAAACTGATGAAGAAAGAGGTGAAGAACGAGGTGGAGAAGCTCCCCCGACAG
CAGCGGAAGGAAAGCATGAAGCAGAAGATGGAGGAGCACACGCAGAAAAAGCAGCTTCTTGACCGGGACTTTGTAGCCAA
GCAGAAGGAGGACCTGGAGCTGGCCATGAAGAGGCTCACCACCGACAACAGGCGGGAGATCTGTGACAAGGAGCGCGAGT
GCCTCATGAAGAAGCAGGAGCTCCTTCGAGACCGGGAAGCAGCCCTGTGGGAGATGGAAGAGCACCAGCTGCAGGAGAGG
CACCAGCTGGTGAAGCAGCAGCTCAAAGACCAGTACTTCCTCCAGCGGCACGAGCTGCTGCGCAAGCATGAGAAGGAGCG
GGAGCAGATGCAGCGCTACAACCAGCGCATGATAGAGCAGCTGAAGGTGCGGCAGCAACAGGAAAAGGCGCGGCTGCCCA
AGATCCAGAGGAGTGAGGGCAAGACGCGCATGGCCATGTACAAGAAGAGCCTCCACATCAACGGCGGGGGCAGCGCAGCT
GAGCAGCGTGAGAAGATCAAGCAGTTCTCCCAGCAGGAGGAGAAGAGGCAGAAGTCGGAGCGGCTGCAGCAACAGCAGAA
ACACGAGAACCAGATGCGGGACATGCTGGCGCAGTGCGAGAGCAACATGAGCGAGCTGCAGCAGCTGCAGAATGAAAAGT
GCCACCTCCTGGTAGAGCACGAAACCCAGAAACTGAAGGCCCTGGATGAGAGCCATAACCAGAACCTGAAGGAATGGCGG
GACAAGCTTCGGCCGCGCAAGAAGGCTCTGGAAGAGGATCTGAACCAGAAGAAGCGGGAGCAGGAGATGTTCTTCAAGCT
GAGCGAGGAGGCGGAGTGCCCAAACCCCTCCACCCCAAGCAAGGCCGCCAAGTTCTTCCCCTACAGCTCTGGGGATGCTT
CC

Fig. 11H

```
STLK6_h   ---------MSLLDCFCTSRTQVESLRPEKQSETSIHQYLVDEPTLSWSR   41
STLK5_h   --------------------------------------------------   0
SPAK_h    MAEPSGSPVHVQLPQQAAPVTAAAAAAPAAATAAPAPAAPAAPAPAPAPA   50

STLK6_h   PSTRASE-VLCSTNVSHYELQVEIGRGFDNLTSVHLARHTPTGTLVTIKI   90
STLK5_h   -----------------------------------------HXEYVPVRR   9
SPAK_h    PAAQAVGWPICRDA---YELQEVIGSGATAV--VQAALCKPRQERVAIKR   95
STLK7_h   -------------NRDDYELQEVIGSGATAV--VQAAYCAPKKEKVAIKR   35

STLK6_h   TNLENCNEERLKALQKAVILSHFFRHPNITTYWTVFTVGSWLWVISPFMA   140
STLK5_h   INLEACSNEMVTS-CRASCMFQTLNHPNIVPYRATLIADNELWVVTSFMA   58
SPAK_h    INLEKCQTSMDELLKEIQAMSQC-SHPNVVTYYTSFVVKDELWLVMKLLS   144
STLK7_h   INLEKCQTSMDELLKEIQAMSQC-HHPNIVSYYTSFVVKDELWLVMKLLS   84

STLK6_h   YGSASQLLRTYFPEG------MSETLIRNILFGAVRGLNYLHQNGCIHRS   184
STLK5_h   YGSAKDLICTHFMDG------MNELAIAYILQGVLKALDYIHHMGYVHRS   102
SPAK_h    GGSMLDIIKYIVNRGEHKNGVLEEAIIATILKEVLEGLDYLHRNGQIHRD   194
STLK7_h   GGSVLDIIKHIVAKGEHKS                                  103

STLK6_h   IKASHILISGDGLVTLSGLSHLHSLVKHGQ--RHRAVYDFPQFSTSVQPW   232
STLK5_h   VKASHILISVDGKVYLSGLRSNLSMISHGQ--RQRVVHDFPKYSVKVLPW   150
SPAK_h    LKAGNILLGEDGSVQIADFGVSAFLATGGDVTRNKVRKTF----VGTPCW   240
```

Fig. 12A

```
STLK6_h   L S P E L L R Q D L H G Y N V K S D I Y S V G I T A C E L A S G Q V P F Q D M H R T Q M L L Q K L K   282
STLK5_h   L S P E V L Q Q N L Q G Y D A K S D I Y S V G I T A C E L A N G H V P F K D M P A T Q M L L E K L N   200
SPAK_h    M A P E V M E Q - V R G Y D F K A D M W S F G I T A I E L A T G A A P Y H K Y P P M K V L M L T L Q   289

STLK6_h   G P P Y S P L D I S I F P Q S E S R M K N S Q S G V D S G I G E S V L V S S G T H T V N S D R L H T   332
STLK5_h   G T V P C L L D T S T I P A E E L T M S P S R S V A N S G L S D S - L T T S T P R P S N G D S P S H   249
SPAK_h    N D P P T - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - L E T G V - - E D   301

STLK6_h   P S - S K T F S P A F F S L V Q L C L Q Q D P E K R P S A S S L L S H V F F K Q M K E E S Q D S I L   381
STLK5_h   P Y - H R T F S P H F H H F V E Q C L Q R N P D A R P S A S T L L N H S F F K Q I K R R A S E A L P   298
SPAK_h    K E M M K K Y G K S F R K L L S L C L Q K D P S K R P T A A E L L K C K F F Q K A K N R E Y - - L I   349

STLK6_h   S L L P P A Y N K P S I S L P P V L P W T E P - - - - - E C D F P D E K D S Y W E F                   418
STLK5_h   E L L R P V - - T P I T N F E G S Q S Q D H S G I F G L V T N L E E L E V D D W E F                   338
SPAK_h    E K L L T R T P D I A Q R A K K V R R V P G S - - - - - S G H L H K T E D G D W E W S D D E M D E K   394

SPAK_h    S E E G K A A F S Q E K S R R V K E E N P E I A V S A S T I P E Q I Q S L S V H D S Q G P P N A N E   444

SPAK_h    D Y R E A S S C A V N L V L R L R N S R K E L N D I R F E F T P G R D T A D G V S Q E L F S A G L V   494

SPAK_h    D G H D V V I V A A N L Q K I V D D P K A L K T L T F K L A S G C D G S E I P D E V K L I G F A Q L   544

SPAK_h    S V S                                                                                                 547
```

Fig. 12B

```
PAK1_h U51120  MSNNGLDIQDKPPAPPMRNTSTMIGAGSKDAGTLNHGSKPLPPNPEEKKKKDRFYRSILP  60
PAK4_h         ------------------------------------------------------------  0
PAK5_h         ------------------------------------------------------------  0

PAK1_h U51120  GDKTNKKKEKERPEISLPSDFEHTIHVGFDAVT-GEFTGMPEQWARLLQTSNITKS----  115
PAK4_h         ---MFRKKKKKRPEISAPQNFQHRVHTSFDPKEGKFVGLPPQWQNILD-TLRRPKPVVDP  56
PAK5_h         ---MF-GKRKKRVEISAPSNFEHRVHTGFDQHEQKFTGLPRQWQSLTEESARRPKPLVDP  56

PAK1_h U51120  ------------------------------------------------------------  115
PAK4_h         SRITRVQLQPMKTVVRGSAMPVDGYISGLLNDIQKLSVISSNTLRGRSPTSRRRAQSLGL  116
PAK5_h         ACITSIQPGAPKTIVRGSKGAKDGALTLLLDEFENMSVTRSNSLRRDSPPPPARAR----  112

PAK1_h U51120  ------------------------------------------------------------  115
PAK4_h         LGDEHWATDPDMYLQSPQSERTDPHGLYLSCNGGTPAGHKQMPWPEPQSPRVLPNGLAAK  176
PAK5_h         -----------------------------------------QENGMPEEPATTARGGPGK  131

PAK1_h U51120  ------------------------------------------------EQKKNPQAVLDV  127
PAK4_h         AQSLGPAEFQGASQRCLQLGACLQSSPPGASPPTGTNRHGMKAAKHGSEEARPQSCLVGS  236
PAK5_h         AGSRGR-----FAGHSEAGGGSGDRRRAGPEKRPKSSREGSGGPQESSRDKRP---LSGP  183

PAK1_h U51120  LEFY-NSKKTSNSQKYMSFTDKS-------AEDYNSSNALNVKA-----VSETPAVPPVS  174
PAK4_h         ATGRPGGEGSPSPKTRESSLKRRLFRSMFLSTAATAPPSSSKPGPPPQSKPNSSFRPPQK  296
PAK5_h         DVGTPQPAGLASGAKLAAG-----RPFNTYPRADTDHPSRGAQGEPHDVAPNGP------  232
```

Fig. 13A

```
PAK1_h U51120  EDEDDDDDDATPPPVIAPRPEHTKSVYTRS----VIEPLPVTPTRDVATSPISPTENNTT 230
PAK4_h         DNPPSLVAKAQSLPSDQPVGTFSPLTTSDTSSPQKSLRTAPATGQLPGRSSPAGSPRTWH 356
PAK5_h         ----------------SAGGLAIPQSSSSSSRPPTRARGAPSPGVL--------GPHASE 268

PAK1_h U51120  P--------------PDALTLNTEKQKKKPKMSDEEILEKLRSIVSVGDPKKKYTRFEKI 276
PAK4_h         AQISTSNLYLPQDPTVAKGA---LAGEDTGVVTHEQFKAALRMVVDQGDPRLLLDSYVKI 413
PAK5_h         PQLAPPA-CTPAAPAVPGPPGPRSPQREPQRVSHEQFRAALQLVVDPGDPRSYLDNFIKI 327

PAK1_h U51120  GQGASGTVYTAMDVATGQEVAIKQMNLQQQPKKELIINEILVMRENKNPNIVNYLDSYLV 336
PAK4_h         GEGSTGIVCLAREKHSGRQVAVKMMDLRKQQRRELLFNEVVIMRDYQHFNVVEMYKSYLV 473
PAK5_h         GEGSTGIVCIATVRSSGKLVAVKKMDLRKQQRRELLFNEVVIMRDYQHENVVEMYNSYLV 387

PAK1_h U51120  GDELWVVMEYLAGGSLTDVVTETCMDEGQIAAVCRECLQALESLHSNQVIHRDIKSDNIL 396
PAK4_h         GEELWVLMEFLQGGALTDIVSQVRLNEEQIATVCEAVLQALAYLHAQGVIHRDIKSDSIL 533
PAK5_h         GDELWVVMEFLEGGALTDIVTHTRMNEEQIAAVCLAVLQALSVLHAQGVIHRDIKSDSIL 447

PAK1_h U51120  LGMDGSVKLTDFGFCAQITPEQSKRSTMVGTPYWMAPEVVTRKAYGPKVDIWSLGIMAIE 456
PAK4_h         LTLDGRVKLSDFGFCAQISKDVPKRKSLVGTPYWMAPEVISRSLYATEVDIWSLGIMVIE 593
PAK5_h         LTHDGRVKLSDFGFCAQVSKEVPRRKSLVGTPYWMAPELISRLPYGPEVDIWSLGIMVIE 507

PAK1_h U51120  MIEGEPPYLNENPLRALYLIATNGTPELQNPEKLSAIFRDFLNRCLEMDVEKRGSAKELL 516
PAK4_h         MVDGEPPYFSDSPVQAMKRLRDSPPPKLKNSHKVSPVLRDFLERMLVRDPQERATAQELL 653
PAK5_h         MVDGEPPYFNEPPLKAMKMIRDNLPPRLKNLHKVSPSLKGFLDRLLVRDPAQRATAAELL 567
```

Fig. 13B

PAK1_h U51120	QHQFLKIAKPLSSLTPLIAAAKEATKNNH	545
PAK4_h	DHPFLLQTGLPECLVPLIQLYRKQTSTC	681
PAK5_h	KHPFLAKAGPPASIVPLMRQNRTR	591

RESIDUES THAT MATCH THE CONSENSUS NAMED CONSENSUS #1 EXACTLY.

BOX RESIDUES THAT MATCH THE CONSENSUS EXACTLY.

Fig. 13C

```
ZC4_h.pro  M A G P G G W R D R E V T D L G H L P D P T G I F S L D K T I G L G T Y G R I Y L G L H E K T G A F   50
ZC1_h.pro  M A N D S P A K S L V D I D L S S L R D P A G I F E L V E V V G N G T Y G Q V Y K G R H V K T G Q L   50

ZC4_h.pro  T A V K V M N A R K D E E E D L R T E L N L L R K Y S F H K N I V S F Y G A F F K L S P P G Q R H Q  100
ZC1_h.pro  A A I K V M D V T E D E E E E I K L E I N M L K K Y S H H R N I A T Y Y G A F I K K S P P G H D D Q  100

ZC4_h.pro  L W M V M E L C A A G S V T D V V R M T S N Q S L K E D W I A Y I C R E I L Q G L A H L H A H R V I  150
ZC1_h.pro  L W L V M E F C G A G S I T D L V K N T K G N T L K E D W I A Y I S R E I L R G L A H L H I H H V I  150

ZC4_h.pro  H R D I K G Q N V L L T H N A E V K L V D F G V S A Q V S R T N G R R N S F I G T P Y W M A P E V I  200
ZC1_h.pro  H R D I K G Q N V L L T E N A E V K L V D F G V S A Q L D R T V G R R N T F I G T P Y W M A P E V I  200

ZC4_h.pro  D C D E D P R R S Y D Y R S D V W S V G I T A I E M A E G A P P L C N L Q P L E A L F V I L R E S A  250
ZC1_h.pro  A C D E N P D A T Y D Y R S D L W S C G I T A I E M A E G A P P L C D M H P M R A L F L I P R N P P  250

ZC4_h.pro  P T V K S S G W S R K F H N F M E K C T I K N F L E R P T S A N M L Q H P F V R D I K N E R H V V E  300
ZC1_h.pro  P R L K S K K W S K K F F S F I E G C L V K N Y M Q R P S T E Q L L K H P F I R D Q P N E R Q V R I  300

ZC4_h.pro  S L T R H L T G I I K K R - - - - - - - - - - - - - - - - - - - - - - - - - - Q K K E Q A R E K K S  324
ZC1_h.pro  Q L K D H I D R T R K K R G E K D E T E Y E Y S G S E E E E E E V P E Q E G E P S S I V N V P G E S  350

ZC4_h.pro  K V S T L R Q A L A K R L S P K R F R A K S S W R P E K L E L S D L E A R R Q R R Q R R W E D I F N  374
ZC1_h.pro  T L R R D F L R L Q Q E N K E R S E A L R R Q Q L L Q E Q Q L R E Q E E Y K R Q L L A E R Q K R I E  400

ZC4_h.pro  Q H E E E L R Q V D K D K E D E S S D N D E V F H S I Q A E V Q I E P L K P Y I S N P K K I E V Q E  424
ZC1_h.pro  Q Q K E Q R R R L E E Q Q R R E R E A R R Q Q E R E Q R R R E Q E E K R R L E E L E R R R K E E E E  450
```

Fig. 14A

```
ZC4_h.pro  RSPSVPNNQDHAHHVKFSSSVPQRSLLEQAQKPIDIRQRSSQNRQNWLAA  474
ZC1_h.pro  RRRAEEEKRRVEREQEYIRRQLEEEQRHLEVLQQQLLQEQAMLLECRWRE  500

ZC4_h.pro  SGDSKHKILAGKTQSYCLTIYISEVKKEEFQEGMNQKCQGAQVGLGPEGH  524
ZC1_h.pro  MEEHRQAERLQRQLQQEQAYLLSLQHDHRRPHPQHSQQPPPPQQERSKPS  550

ZC4_h.pro  CIWQLGESSSEEESPVTGRRSQSSPPYSTIDQKLLVDIHVPDGFKVGKIS  574
ZC1_h.pro  FHAPEPKAHYEPADRAREVEDRFRKTNHSSPEAQSKQTGRVLEPPVPSRS  600

ZC4_h.pro  PPVYLTNEWVGYNALSEIFRNDWLTPAPVIQPPEEDGDYVELYDASADTD  624
ZC1_h.pro  ESFSNGNSESVHPALQRPAEPQVPVRTTSRSPVLSRRDSPLQGSGQQNSQ  650

ZC4_h.pro  GDDDDESNDTFEDTYDHANGNDDLDNQVDQANDVCKDHDDDNNKFVDDVN  674
ZC1_h.pro  AGQRNSTSIEPRLLWERVEKLVPRPGSGSSSGSSNSGSQPGSHPGSQSGS  700

ZC4_h.pro  NNYYEAPSCPRASYGRDGSCKQDGYDGSRGKEEAYRGYGSHTANRSHGGS  724
ZC1_h.pro  GERFRVRSSSKSEGSPSQRLENAVKKPEDKKEVFRPLKPADLTALAKELR  750

ZC4_h.pro  AASEDNAAIGDQEEHAANIGSERRGSEGDGGKGVVRTSEESGALGLNGEE  774
ZC1_h.pro  AVEDVRPPHKVTDYSSSSEESGTTDEEDDDVEQEGADESTSGPEDTRAAS  800

ZC4_h.pro  NLSEIDGPGLKRPASQDFEYLQEEPGGGNEASNAIDSGAAPSAPDHESDN  824
ZC1_h.pro  SLNLSNGETESVKTMIVHDDVESEPAMTPSKEGTLIVRRTQSASSTLQKH  850

ZC4_h.pro  KDISESSTQSDFSANHSSPSKGSGMSADANFASAILYAGFVEVPEESPKQ  874
ZC1_h.pro  KSSSSFTPFIDPRLLQISPSSGTTVTSVVGFSCDGMRPE--AIRQDPTRK  898
```

Fig. 14B

```
ZC4_h.pro  PSEVNVNPLYVSPACKKPLIHMYEKEFTSEICCGSLWGVNLLLGTRSNLY  924
ZC1_h.pro  GSVVNVNPTNTRPQSDTPEIRKYKKRFNSEILCAALWGVNLLVGTESGLM  948

ZC4_h.pro  LMDRSGKADITKLIRRRPFRQIQVLEPLNLLITISGHKNRLRVYHLTWLR  974
ZC1_h.pro  LLDRSGQGKVYPLINRRRFQQMDVLEGLNVLVTISGKKDKLRVYYLSWLR  998

ZC4_h.pro  NKILNNDPESKRRQE-EMLKTEEACKAIDKLTGCEHFSVLQHEETTYIAI  1023
ZC1_h.pro  NKILHNDPEVEKKQGWT---------TVGDLEGCVHYKVVKYERIKFLVI  1039

ZC4_h.pro  ALKSSIHLYAWAPKSFDESTAIKVFPTLDHKPVTVDLAIGSEKRLKIFFS  1073
ZC1_h.pro  ALKSSVEVYAWAPKPYHKFMAFKSFGELVHKPLLVDLTVEEGQRLKVIYG  1089

ZC4_h.pro  SADGYHLIDAESEVMSDVTLPKNPLEIIIPQNIIILPDCLGIGMMLTENA  1123
ZC1_h.pro  SCAGFHAVDVDSGSVYDIYLPTHIQCSIKPHAIIILPNTDGMELLVCYED  1139

ZC4_h.pro  EALSVEANEQLFKKILEMWKDIPSSIAFECTQRTTGWGQKAIEVRSLQSR  1173
ZC1_h.pro  EGVYVNTYGRITKDVVLQWGEMPTSVAYIRSNQTMGWGEKAIEIRSVETG  1189

ZC4_h.pro  VLESELKRRSIKKLRFLCTRGDKLFFTSTLRNHHSRVYFMTLGKLEELQS  1223
ZC1_h.pro  HLDGVFMHKRAQRLKFLCERNDKVFFASVRSGGSSQVYFMTLGRTSLLSW  1239

ZC4_h.pro  NYDV                                                1227
ZC1_h.pro                                                      1239
```

BOX RESIDUES THAT MATCH ZC4_h.pro EXACTLY.

Fig. 14C

```
Db = LOK1_m
Qy = GEK2_h
            *********************************.**************************
Db      1 MAFANFRRILRLSTFEKRKSREYEHVRRDLDPNDVWEIVGELGDGAFGKVYKAKNKETGA 60
Qy      1 MAFANFRRILRLSTFEKRKSREYEHVRRDLDPNEVWEIVGELGDGAFGKVYKAKNKETGA 60

            *****************************************************************
Db     61 LAAAKVIETKSEEELEDYIVEIEILATCDHPYIVKLLGAYYYDGKLWIMIEFCPGGAVDA 120
Qy     61 LAAAKVIETKSEEELEDYIVEIEILATCDHPYIVKLLGAYYHDGKLWIMIEFCPGGAVDA 120

            *****************************.******************************
Db    121 IMLELDRGLTEPQIQVVCRQMLEALNFLHGKRIIHRDLKAGNVLMTLEGDIRLADFGVSA 180
Qy    121 IMLELDRGLTEPQIQVVCRQMLEALNFLHSKRIIHRDLKAGNVLMTLEGDIRLADFGVSA 180

            ************************.******.****************************
Db    181 KNLKTLQKRDSFIGTPYWMAPEVVLCETMKDAPYDYKADIWSLGITLIEMAQIEPPHHEL 240
Qy    181 KNLKTLQKRDSFIGTPYWMAPEVVMCETMKDTPYDYKADIWSLGITLIEMAQIEPPHHEL 240

            *************************************************.*****  ***
Db    241 NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLQHPFVSRVTSN 300
Qy    241 NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLEHPFVSSITSN 300

            **********************..*********.  * ****.*..*. ***...* *..
Db    301 KALRELVAEAKAEVMEEIEDGREDGEEEDAVDAVPPLVNHTQDSANVTQPSLDSNKLLQD 360
Qy    301 KALRELVAEAKAEVMEEIEDGRDEGEEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEE 360
```

Fig. 15A

```
       * ****.***.*..** ******** .******..    *.* * **********.****
Db 361 S-STPLPPSQPQEPVNGPCSQPSGDGPLQTTSPADGLSKNDNDLKVPVPLRKSRPLSMDA 419
Qy 361 SPSTPLAPSQSQDSVNEPCSQPSGDRSLQTTSPPVVAPGNENGLAVPVPLRKSRPVSMDA 420

       ***. .***...*  . ****..****.*************** *.**.** *.  .*.
Db 420 RIQMDEEKQIPDQDENPSPAASKSQKANQSRPNSSALETLGGEALTNGGLELPSSVTPSH 479
Qy 421 RIQVAQEKQVAEQGGDLSPAANRSQKASQSRPNSSALETLGGEKLANGSLEPPAQAAPGP 480

       *** ****.* *********.**.******* ****.* .** .*******.********
Db 480 SKRASDCSNLSTSESMDYGTSLSADLSLNKETGSLSLKGSKLHNKTLKRTRRFVVDGVEV 539
Qy 481 SKRDSDCSSLCTSESMDYGTNLSTDLSLNKEMGSLSIKDPKLYKKTLKRTRKFVVDGVEV 540

       ********************************************.***************
Db 540 SITTSKIISEDEKKDEEMRFLRRQELRELRLLQKEEHRNQTQLSSKHELQLEQMHKRFEQ 599
Qy 541 SITTSKIISEDEKKDEEMRFLRRQELRELRLLQKEEHRNQTQLSNKHELQLEQMHKRFEQ 600

       ********.* ********************.***.***.**********..****** *
Db 600 EINAKKKFYDVELENLERQQKQQVEKMEQDHSVRRKEEAKRIRLEQDRDYAKFQEQLKQM 659
Qy 601 EINAKKKFFDTELENLERQQKQQVEKMEQDHAVRRREEARRIRLEQDRDYTRFQEQLKLM 660

       *****.*********************.**** *****************..***.****
Db 660 KKEVKSEVEKLPRQQRKESMKQKMEEHSQKKQRLDRDFVAKQKEDLELAMRKLTTENRRE 719
Qy 661 KKEVKNEVEKLPRQQRKESMKQKMEEHTQKKQLLDRDFVAKQKEDLELAMKRLTTDNRRE 720
```

Fig. 15B

```
                ******.** *****************************************.********
Db    720 ICDKERDCLSKKQELLRDREAALWEMEEHQLQERHQLVKQQLKDQYFLQRHDLLRKHEKE 779
Qy    721 ICDKERECLMKKQELLRDREAALWEMEEHQLQERHQLVKQQLKDQYFLQRHELLRKHEKE 780

          ***********.********************.* **************.***.******
Db    780 REQMQRYNQRMMEQLKVRQQQEKARLPKIQRSDGETRMAMYKKSLHINGAGSASEQREKI 839
Qy    781 REQMQRYNQRMIEQLKVRQQQEKARLPKIQRSEGKTRMAMYKKSLHINGGGSAAEQREKI 840

          ************.**********.*****.******************************
Db    840 KQFSQQEEKRQKAERLQQQQKHEHQMRDMVAQCESNMSELQQLQNEKCYLLVEHETQKLK 899
Qy    841 KQFSQQEEKRQKSERLQQQQKHENQMRDMLAQCESNMSELQQLQNEKCHLLVEHETQKLK 900

          ********.************************************* * *.*****..**
Db    900 ALDESHNQSLKEWRDKLRPRKKALEEDLNQKKREQEMFFKLSEEAE-PRPTTPSKASNFF 958
Qy    901 ALDESHNQNLKEWRDKLRPRKKALEEDLNQKKREQEMFFKLSEEAECPNPSTPSKAAKFF 960

          ********
Db    959 PYSSGDAS                                                     966
Qy    961 PYSSGDAS                                                     968
```

Fig. 15C

SEQUENCE LISTING

<110> SUGEN, INC.

<120> STE20-RELATED PROTEIN KINASES

<130> 240/300-PCT

<140> TO BE ASSIGNED
<141> Herewith

<150> US 60/081,784
<151> 1998-04-14

<160> 147

<170> FastSEQ for Windows Version 3.0

<210> 1
<211> 3268
<212> DNA
<213> Mammalian (Human) STLK2

<400> 1

taacagccca cctcctagcc ccgggctacg cgccgccagc ccagtaaccc cacttttgtg 60
tgtcctccca ggcccccgatc gaaaagcctg ggagggccgc cgaactaccc ccggagggag 120
gagccagtcc gaacccaagg cgccaccgcc gcagaagcgg agcgaggcag cattcgcctc 180
catggcccac tcgccggtgg ctgtccaagt gcctgggatg cagaataaca tagctgatcc 240
agaagaactg ttcacaaaat tagagcgcat tgggaaaggc tcatttgggg aagttttcaa 300
aggaattgat aaccgtaccc agcaagtcgt tgctattaaa atcatagacc ttgaggaagc 360
cgaagatgaa atagaagaca ttcagcaaga aataactgtc ttgagtcaat gtgacagctc 420
atatgtaaca aaatactatg ggtcatattt aaaggggtct aaattatgga taataatgga 480
atacctgggc ggtggttcag cactggatct tcttcgagct ggtccatttg atgagttcca 540
gattgctacc atgctaaagg aaattttaaa aggtctggac tatctgcatt cagaaaagaa 600
aattcaccga gacataaaag ctgccaatgt cttgctctca gaacaaggag atgttaaact 660
tgctgatttt ggagttgctg gtcagctgac agatacacag attaaaagaa ataccttttgt 720
gggaactcca ttttggatgg ctcctgaagt tattcaacag tcagcttatg actcaaaagc 780
tgacatttgg tcattgggaa ttactgctat tgaactagcc aagggagagc cacctaactc 840
cgatatgcat ccaatgagag ttctgtttct tattcccaaa aacaatcctc caactcttgt 900
tggagacttt actaagtctt ttaaggagtt tattgatgct tgcctgaaca aagatccatc 960
atttcgtcct acagcaaaag aacttctgaa acacaaattc attgtaaaaa attcaaagaa 1020
gacttcttat ctgactgaac tgatagatcg ttttaagaga tggaaggcag aaggacacag 1080
tgatgatgaa tctgattccg agggctctga ttcggaatct accagcaggg aaaacaatac 1140
tcatcctgaa tggagcttta ccaccgtacg aaagaagcct gatccaaaga aagtacagaa 1200
tggggcagag caagatcttg tgcaaaccct gagttgtttg tctatgataa tcacacctgc 1260
atttgctgaa cttaaacagc aggacgagaa taacgctagc aggaatcagg cgattgaaga 1320
actcgagaaa agtattgctg tggctgaagc cgcctgtccc ggcatcacag ataaaatggt 1380
gaagaaacta attgaaaaat ttcaaaagtg ttcagcagac gaatcccccct aagaaactta 1440

```
ttattggctt ctgtttcata tggacccaga gagccccacc aaacctacgt caagattaac   1500
aatgcttaac ccatgagctc catgtgcctt ttggatcttt gcaacactga agatttggaa   1560
gaagctatta aactattttg tgatggcgtt tatcatttta tattttgaaa ggattatttt   1620
gtaaggaata acttttaata ctatagtttc acctgtattc tagtaaatgt tgagacaccg   1680
ttttgctttt aagtatccct atttcttaag ttacgaggat gaataccttt cacattttga   1740
tctttagttg actctacagt catgaaacat acaggtcttt caaagtcatt ctcaatattc   1800
agcttttgta aattatcaag cttcaaaaag cttttttta aaaaaaaaaa catgcatatt   1860
ctaaaaatga ctattggtgg ggaggtgtaa ataagtcata ccttcttaaa acagaaaatt   1920
taagtaaagt cttttaaatg aaacctgtaa aagtattgac tcttctacca agttggtatg   1980
atattccagg cagctcaatg attatcacat ttgagaccct gtgtttgaag catttacagg   2040
caatgtacag caacagaggt acctcttggt gtatagtatt tacattctct tttaggtaga   2100
agaggcaatt ttacccttat ttcacatggt tagaaattta aagcaagatc atttacccaa   2160
ggataggtgt ttggtaatgt tgaaggagtt agtctggctt catgttttac atcttcaact   2220
aaaatcccat actatctgct tggatttgga gagccaaaaa ataaagctga ttgtcatgtg   2280
attaaatatc tgatcaacag gtatgaatat aacttaaatc agcatatttt tgccatggta   2340
ataaattgtc ctataaacta tttatatatt tttgttcttc ataattatca ctaataagca   2400
tcagtttgtt gtttttaaaa ggatatttaa gtgagcattt tctagttcat atgaaaataa   2460
ccatagtaca ggatgatttc tgtccacaca aaggttaaat tagattgcac agttaatttt   2520
cacttatatt tatggtacta ttatgtgggt gatgcctttt tcttttaagc ccagtacata   2580
tattatgcct gcctaagttc tgaactgggg ctgtatttca gtagttgtag aattattgat   2640
atttagtttt gatagctaat gtttaattgt ttggatctgc acagtttggt ttttgcacaa   2700
aagtcattta aaaaaatctg agtaattgtc aaatattaaa agaaagatat tcttcctgta   2760
aggaatacag tttttagtca aagtggccat tacatcctct ttttaattta cataatacag   2820
atacttgaga aagttgttgt ggtgttgtat gccaagaaaa ttctttttat tggtgcctat   2880
attgtaacaa ttatttttaa tgcattgtat tttgaagtaa cggttcagtt aaatttttca   2940
cctgctgtgt aactgaaaca caattacagt ttataatcat ctgtagaagt ctggagataa   3000
ttttgcaact catgttatgg gttaaatgaa tatttttgta aaagtaaaag caacaaattt   3060
ataaattgat tatttgaaac tttacaacac aattgcatcc caaatacaaa ttgtattgct   3120
tattcattat agctattcgt cctgtaatct gtttctaggt gaagcatact ccagtgtttt   3180
aggggttttg aaaataaata tttaaatttc acagtcaaaa aaaaaaaaaa aaaaaaaaaa   3240
aaaaaaaaaa aaaaaaaaaa aaaaaaa                                       3268
```

<210> 2
<211> 3030
<212> DNA
<213> Mammalian (Human) STLK3

<400> 2

```
gacagcagcg ccggccccgg cagctcccgc ggccccggcc ccggccccgg ccccggcccc     60
ggcggcacag gctgtcggct ggcccatctg cagggacgcg tacgagctgc aggaggttat    120
cggcagtgga gctactgctg tggttcaggc agccctatgc aaacccaggc aagaacgtgt    180
agcaataaaa cggatcaact tggaaaaatg ccagaccagt atggatgaac tattaaaaga    240
aattcaagcc atgagtcagt gcagccatcc caacgtagtg acctattaca cctcttttgt    300
ggtcaaagat gaactttggc tggtcatgaa attactaagt ggaggttcaa tgttggatat    360
cataaaatac attgtcaacc gaggagaaca caagaatgga gttctggaag aggcaataat    420
agcaacaatt cttaaagagg ttttggaagg cttagactat ctacacagaa acggtcagat    480
tcacagggat ttgaaagctg gtaatattct tctgggtgag gatggttcag tacaaatagc    540
agattttggg gtaagtgcgt tcctagcaac agggggtgat gttacccgaa ataaagtaag    600
aaaaacattc gttggcaccc catgttggat ggctcctgaa gtcatggaac aggtgagagg    660
ctatgacttc aaggctgaca tgtggagttt tggaataact gccattgaat tagcaacagg    720
agcagcgcct tatcacaaat atcctcccat gaaagtgtta atgttgactt tgcaaaatga    780
tccacccact ttggaaacag ggtagagga taaagaaatg atgaaaaagt acggcaagtc    840
ctttagaaaa ttactttcac tgtgtcttca gaaagatcct tccaaaaggc ccacagcagc    900
```

agaactttta aaatgcaaat tcttccagaa agccaagaac agagagtacc tgattgagaa 960
gctgcttaca agaacaccag acatagccca aagagccaaa aaggtaagaa gagttcctgg 1020
gtcaagtggt caccttcata aaaccgaaga cggggactgg gagtggagtg acgacgagat 1080
ggatgagaag agcgaagaag ggaaagcagc tttttctcag gaaaagtcac gaagagtaaa 1140
agaagaaaat ccagagattg cagtgagtgc cagcaccatc cccgaacaaa tacagtccct 1200
ctctgtgcac gactctcagg gcccacccaa tgctaatgaa gactacagag aagcttcttc 1260
ttgtgccgtg aacctcgttt tgagattaag aaactccaga aaggaactta atgacatacg 1320
atttgagttt actccaggaa gagatacagc agatggtgta tctcaggagc tcttctctgc 1380
tggcttggtg gatggtcacg atgtagttat agtggctgct aatttacaga agattgtaga 1440
tgatcccaaa gctttaaaaa cattgacatt taagttggct tctggctgtg atgggtcgga 1500
gattcctgat gaagtgaagc tgattgggtt tgctcagttg agtgtcagct gatgtatgtc 1560
ccttgatgtc accctgatct gtcatgcccc accgccaccc ctactccctt caaccctccc 1620
tctttctgcc catttcctcc caccccctca ctcccatttc ctagcaaaat cagaagattg 1680
tgaagaggcc ggcttcaaca aaatgggata aaaaaataat tttttaaaac ttacaacact 1740
ccgagttctg ctttattctc tagcaatcca cagtacaaga acaagcaaat gccacagctg 1800
cacgactgtt gctcattttt ccaaaagcta tttaatattc ttagcaatca atttggatat 1860
cccttaagtg aaaagaatct gaaatacact caggtggtct tatttattgg caacaaaagg 1920
aattttctat ccagaagcct atttctcctt tcattgttgt tatttctgtt ataatacttt 1980
aattgtacat ctgacaatac tgcctctttt atgttgtatt tagaaattaa tatacttata 2040
aaattaagat ttattagcca aacttgaatt ctagttttaa aactgactgt gaatttttatt 2100
tttcatatat ttatgcatta cacaccttag ctataagaaa aaaagggttt tgattatatg 2160
cttcttgcag ttaatctcgt tatttaaaca aaaagttttg ggtctatctt tggagtattt 2220
gtaacttcta aattttgaaa tgactgaatt aggaatttgg atgcttattc ttttagtctg 2280
tttgcctaaa aaccaattta caatctgact gtctcttggg agagggaggt gccttgcaaa 2340
ctttcacatt aagaatgtgc ctgaggctgc tttactctgg aatagtctca gatctaaaat 2400
ttcctctata taaggtggca tatgttaagt tttgcttcat tggaccgttt agaatgctat 2460
gtaaaatgtt gccattctgt tagattgcta actatatacc catctctgat ttggctctcc 2520
ttaagtgata ggatttgtta ttctaaaggt gataaacttg aaaatatcag aatctgagtt 2580
ttacttgaaa ttttgcagaa tacccaggtg gagtgaaaat tggaagggtt ttgtgcaatg 2640
actaaaaggt aaaacgctgt taaggttcaa gaatcaatac tttcaaccca agtagccctc 2700
tgcttgactg tatattatgg aactagtaaa ccttaggatt ttgaaaattg gagtctaatc 2760
tttcaaggag gtgggctccc aggatggtac cattgctctt tcctagctaa ccctagatat 2820
ggcagctctt taatgtactt caaaaagcaa atatatatta ctaaggaaaa aaagttattt 2880
ataattgcct tgtcataatt gttaaggtgt tctagagcca tttgcataca atttaatgta 2940
atttcattcc attctattgt ttacacaacg attactcgaa gatgactgca aaggtaaaag 3000
gaaaataaaa gtgtattgca caatgaaaaa 3030

<210> 3
<211> 3857
<212> DNA
<213> Mammalian (Human) STLK4

<400> 3

caaaagtgga gtcctagatg antctaccat tgctacgata ctccgagaag tactggaagg 60
gctggaatat ctgcataaaa ntggacagat ccacagagat gtgaaagctg gaaacattct 120
tnttggagaa gatggctcag tacagatttc agactttggg gttagtgctt ttttagcaac 180
tggtggtgat attacccgaa ataaagtgag aaagaccttt gttggcaccc cttgttggat 240
ggcacctgaa gttatggaac aggtccgtgg ttatgatttc aaagctgata tttggagttt 300
tggaattaca gcaattgaat tggctacagg ggcggctcct tatcataaat atccaccaat 360
gaaggtttta atgctgacac tgcagaacga tcctccttct ttggaaactg gtgttcaaga 420
taaagaaatg ctgaaaaaat atggaaaatc atttagaaaa atgatttcat tgtgccttca 480
aaaagatcca gaaaaaagac caacagcagc agaactatta aggcacaaat tttccagaa 540
agcaaagaat aaagaatttc ttcaagaaaa aacattgcag agagcaccaa ccatttctga 600

aagagcaaaa aaggttcgga gagtaccagg ttccagtggg cgtcttcata agacagagga 660
tggaggctgg gagtggagtg atgatgaatt tgatgaagaa agtgaggaag ggaaagcagc 720
aatttcacaa ctcaggtctc cccgagtgaa agaatcaata tcaaattctg agctctttcc 780
aacaactgat cctgtgggta ctttgctcca agttccagaa cagatctctg ctcatctacc 840
tcagccagct gggcagattg ctacacagcc aactcaagtc tctctcccac ccaccgcaga 900
gccagcaaaa acagctcagg ctttgtcttc aggatcaggt tcacaagaaa ccaagatccc 960
aatcagtcta gtactaagat taaggaattc caaaaaagaa ctaaatgata ttcgatttga 1020
atttactcct gggagagata cagcagaggg tgtctctcag gaactcattt ctgctggcct 1080
ggtcgacgga agggatttag taatagtggc agctaatttg cagaaaattg tggaagaacc 1140
tcagtcaaat cgatctgtca ctttcaaact ggcatctggt gtcgaaggct cagatattcc 1200
tgatgatggt aaactgatag gatttgccca gctcagcatc agctaaacca caaccctgga 1260
agaggcggcc taaggagatt ccacacatgc gtatctctgt tgcttctatt ggcctaaacc 1320
cactactgcc aaagaaccca gcaacaaacc tcccggctag gagctttaga agtctttatg 1380
ttcttcctgc catcattcct ccttttccca cagggaaaga aaagttggat cactagtggc 1440
cagcatcccc agagttccgt tagtaaactt acttcatatg tcccctgtct tcctccatct 1500
gagaagtggc ccatgtgctt caaggcccag gagggagatc tgtcagctca ttcttgcctt 1560
actccaatga tggcccaggt ggaaaagtag cagctgtatc gggcttcctc atcctgcctg 1620
ttcccccaca cctgccagga tatggacatc ttgggatatc tctttaccac tgaagtagaa 1680
ttgattgttc agctggagcc cagagaattt aatttaatgt tttttctttg tacctgatgt 1740
gaattctagc aacctttgtt aggaaaaagc acagcctcag atggaggcag cctaaactgt 1800
gttcttgttt tgttcatggt gtttctaagc gttttgctga agctgctctc aggcaccccc 1860
ttcttcattg ctctctccag aaagggttgc tagccttaac ttcagctggt gcaaaacatc 1920
tgactgtagc cgaacttcag ccatcagatc cttcaaagtg gaactttgga ttgtttttac 1980
agacaacatc gagtaatggc ttgtaaatgt gaattttgcc agaggtggtt tttgaacagg 2040
aaaatcataa ttcatatcat tggagaagta tttattttca aatatcaaat tgaagaaaaa 2100
ctcaatcctc ccatgaaaat cagttcgcct ggcctccaag tcgtgaggaa atgggtatgc 2160
aaggctgaga tttctacagc aataaaggag acacacactg ggccagagag gcctgccttc 2220
tgcctgctct cctgcactga ccctttggag gggtctctg tgtgctgaag ctaactcaag 2280
atggaaagtg aaaccacatg tgccgtgacc tttaggtttt atgagtagac agtgttcatt 2340
tgattttcta cagaaataat ataaattatt ctttaggttt aaaaaagagc actcataatg 2400
caatatgtga ataatcagtg aggttgattt ttctttttc ctaccgtttc atagtctttg 2460
tctaactgct agtaacccta ccgagtttta tatatgagtg ggatactcaa tctggcctta 2520
aaaagataca caaagatggg ctgtgggtcc ctggaaaggg ggagagttgc cctttacaga 2580
atcactcgag ccctttccag cactgttggt ctgatgaaca aggttgtttt accttatttt 2640
ctcttggaac atatctgaaa accttcccca caaataactt gtcacacctt ttgtttcatt 2700
ctgagtcttt agttttagtc atgggctttc ttcacctgct ctaggtgcaa aggcatgttg 2760
ggaaagagat ggatgttggg gaggaagaga ggagatggat ttcagttggg agttaggagg 2820
agagtaggtg agatgatcag acaccggagt tcaacgtccc agcagtcttg gtaaaaggag 2880
ggagcctgct gagccaggag ggagaaaaga agattgacca gcttgctaga aaaatactta 2940
gcttttcttt ttcttttttt gtggaggggg gacggagagg aacaaggatg gggaggtagg 3000
aatgaggtat agaaaagaga tagcatcttc tttggcacaa gactagtggc ttaccgctta 3060
ccttagagtt ttgttttttt tttttcaaac ccatcaaaat ctacttattt atgaatccaa 3120
ggggtggcag catcactctg ttctagcatt ctttgtggag atggtctggt gcctagctgg 3180
gagtgagcag cagcccatcc cctgttcact ttctctagcc catcattacc tgtgaactgc 3240
agtggggcag tcatggcaaa tagaattggg ctggggtttc tccttctttt cagttcattg 3300
tttgccctgc taggaattag aagacagaca ccatgtccca ggacagtgtt acttcttctg 3360
catgatgtgt ggtagactcc ctttgctggc ttgtgcagtg atactgagaa aatacatgaa 3420
cagaaactgc ccaggtggaa cagcacgtaa cctagtgagt gactgtactc ctttctagga 3480
atgctgattc agagtgcacc tctttgacta ggtcccagga tccccttgtc cctggagtag 3540
ggactaacta tagcacaaag taatatgtgc caatgctatt tgtgaaatgt ttggtctttc 3600
taaacgacta aaggatttgt tgggtttttg cttaagtttt gaaccaaatc ctagagccag 3660
ctgataatat ttaataatct ggaggagaga ataatgatgt accaataagt ggagattcct 3720
ccttatgatg tatgctaggt tatggaagat gtaaaatatt caactttttc ctccttttt 3780
tggactttgt attttactgc atgttttctt catttttaat caataaagag taaattgtca 3840
aaaaaaaaaa aaaaaaa 3857

<210> 4
<211> 1584
<212> DNA
<213> Mammalian (Human) STLK5

<400> 4

ctcatctgta cacacttcat ggatggcatg aatgagctgg cgattgctta catcctgcag 60
ggggtgctga aggccctcga ctacatccac cacatgggat atgtacacag gagtgtcaaa 120
gccagccaca tcctgatctc tgtggatggg aaggtctacc tgtctggttt gcgcagcaac 180
ctcagcatga taagccatgg gcagcggcag cgagtggtcc acgattttcc caagtacagt 240
gtcaaggttc tgccgtggct cagccccgag gtcctccagc agaatctcca gggttatgat 300
gccaagtctg acatctacag tgtgggaatc acagcctgtg aactggccaa cggccatgtc 360
ccctttaagg atatgcctgc cacccagatg ctgctagaga aactgaacgg cacagtgccc 420
tgcctgttgg ataccagcac catccccgct gaggagctga ccatgagccc ttcgcgctca 480
gtggccaact ctggcctgag tgacagcctg accaccagca ccccccggcc ctccaacggt 540
gactcgccct cccaccccta ccaccgaacc ttctcccccc acttccacca ctttgtggag 600
cagtgccttc agcgcaaccc ggatgccagg cccagtgcca gcaccctcct gaaccactct 660
ttcttcaagc agatcaagcg acgtgcctca gaggctttgc ccgaattgct tcgtcctgtc 720
acccccatca ccaattttga gggcagccag tctcaggacc acagtggaat ctttggcctg 780
gtaacaaacc tggaagagct ggaggtggac gattgggagt tctgagcctc tgcaaactgt 840
gcgcattctc cagccaggga tgcagaggcc acccagaggc ccttcctgag ggccggccac 900
attcccgccc tcctgggcag attgggtaga aaggacattc ttccaggaaa gttgactgct 960
gactgattgg gaaagaaaat cctggagaga tacttcactg ctccaaggct tttgagacac 1020
aagggaatct caacaaccag ggatcaggag ggtccaaagc cgacattccc agtcctgtga 1080
gctcaggtga cctcctccgc agaagagaga tgctgctctg gccctgggag ctgaattcca 1140
agcccagggt ttggctcctt aaacccgagg accgccacct cttcccagtg cttgcgacca 1200
gcctcattct atttaacttt gctctcagat gcctcagatg ctataggtca gtgaaagggc 1260
aagtagtaag ctgcctgcct cccttccctc agacctctcc ctcataattc cagagaaggg 1320
catttctgtc tttttaagca cagactaagg ctggaacagt ccatccttat ccctcttctg 1380
gcttgggccc tgacacctaa gtctttccca cggtttatgt gtgtgcctca ttcctttccc 1440
accaagaatc catcttagcg cctcctgcca gctgccctgg tgctttctcc aagggccatc 1500
agtgtcttgc ctagcttgag ggcttaagtc cttatgctgt gttagtttcg ttgtcagaac 1560
aaattaaaat tttcagagac gctg 1584

<210> 5
<211> 416
<212> PRT
<213> Mammalian (Human) STLK2

<400> 5

Met Ala His Ser Pro Val Ala Val Gln Val Pro Gly Met Gln Asn Asn
1 5 10 15

Ile Ala Asp Pro Glu Glu Leu Phe Thr Lys Leu Glu Arg Ile Gly Lys
20 25 30

Gly Ser Phe Gly Glu Val Phe Lys Gly Ile Asp Asn Arg Thr Gln Gln
35 40 45

Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala Glu Asp Glu Ile
50 55 60

Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser Gln Cys Asp Ser Ser
65 70 75 80

Tyr Val Thr Lys Tyr Tyr Gly Ser Tyr Leu Lys Gly Ser Lys Leu Trp
85 90 95

Ile Ile Met Glu Tyr Leu Gly Gly Gly Ser Ala Leu Asp Leu Leu Arg
100 105 110

Ala Gly Pro Phe Asp Glu Phe Gln Ile Ala Thr Met Leu Lys Glu Ile
115 120 125

Leu Lys Gly Leu Asp Tyr Leu His Ser Glu Lys Lys Ile His Arg Asp
130 135 140

Ile Lys Ala Ala Asn Val Leu Leu Ser Glu Gln Gly Asp Val Lys Leu
145 150 155 160

Ala Asp Phe Gly Val Ala Gly Gln Leu Thr Asp Thr Gln Ile Lys Arg
165 170 175

Asn Thr Phe Val Gly Thr Pro Phe Trp Met Ala Pro Glu Val Ile Gln
180 185 190

Gln Ser Ala Tyr Asp Ser Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr
195 200 205

Ala Ile Glu Leu Ala Lys Gly Glu Pro Pro Asn Ser Asp Met His Pro
210 215 220

Met Arg Val Leu Phe Leu Ile Pro Lys Asn Asn Pro Pro Thr Leu Val
225 230 235 240

Gly Asp Phe Thr Lys Ser Phe Lys Glu Phe Ile Asp Ala Cys Leu Asn
245 250 255

Lys Asp Pro Ser Phe Arg Pro Thr Ala Lys Glu Leu Leu Lys His Lys
260 265 270

Phe Ile Val Lys Asn Ser Lys Lys Thr Ser Tyr Leu Thr Glu Leu Ile
275 280 285

Asp Arg Phe Lys Arg Trp Lys Ala Glu Gly His Ser Asp Asp Glu Ser
290 295 300

Asp Ser Glu Gly Ser Asp Ser Glu Ser Thr Ser Arg Glu Asn Asn Thr
305 310 315 320

His Pro Glu Trp Ser Phe Thr Thr Val Arg Lys Lys Pro Asp Pro Lys
325 330 335

Lys Val Gln Asn Gly Ala Glu Gln Asp Leu Val Gln Thr Leu Ser Cys
340 345 350

Leu Ser Met Ile Ile Thr Pro Ala Phe Ala Glu Leu Lys Gln Gln Asp
355 360 365

Glu Asn Asn Ala Ser Arg Asn Gln Ala Ile Glu Glu Leu Glu Lys Ser
370 375 380

Ile Ala Val Ala Glu Ala Ala Cys Pro Gly Ile Thr Asp Lys Met Val
385 390 395 400

Lys Lys Leu Ile Glu Lys Phe Gln Lys Cys Ser Ala Asp Glu Ser Pro
405 410 415

<210> 6
<211> 516
<212> PRT
<213> Mammalian (Human) STLK3

<400> 6

Thr Ala Ala Pro Ala Pro Ala Ala Pro Ala Ala Pro Ala Pro Ala Pro
1 5 10 15

Ala Pro Ala Pro Ala Ala Gln Ala Val Gly Trp Pro Ile Cys Arg Asp
20 25 30

Ala Tyr Glu Leu Gln Glu Val Ile Gly Ser Gly Ala Thr Ala Val Val
35 40 45

Gln Ala Ala Leu Cys Lys Pro Arg Gln Glu Arg Val Ala Ile Lys Arg
50 55 60

Ile Asn Leu Glu Lys Cys Gln Thr Ser Met Asp Glu Leu Leu Lys Glu
65 70 75 80

Ile Gln Ala Met Ser Gln Cys Ser His Pro Asn Val Val Thr Tyr Tyr
85 90 95

Thr Ser Phe Val Val Lys Asp Glu Leu Trp Leu Val Met Lys Leu Leu
100 105 110

Ser Gly Gly Ser Met Leu Asp Ile Ile Lys Tyr Ile Val Asn Arg Gly
115 120 125

Glu His Lys Asn Gly Val Leu Glu Glu Ala Ile Ile Ala Thr Ile Leu
130 135 140

Lys Glu Val Leu Glu Gly Leu Asp Tyr Leu His Arg Asn Gly Gln Ile
145 150 155 160

His Arg Asp Leu Lys Ala Gly Asn Ile Leu Leu Gly Glu Asp Gly Ser
165 170 175

Val Gln Ile Ala Asp Phe Gly Val Ser Ala Phe Leu Ala Thr Gly Gly
180 185 190

Asp Val Thr Arg Asn Lys Val Arg Lys Thr Phe Val Gly Thr Pro Cys
195 200 205

Trp Met Ala Pro Glu Val Met Glu Gln Val Arg Gly Tyr Asp Phe Lys
210 215 220

Ala Asp Met Trp Ser Phe Gly Ile Thr Ala Ile Glu Leu Ala Thr Gly
225 230 235 240

Ala Ala Pro Tyr His Lys Tyr Pro Pro Met Lys Val Leu Met Leu Thr
245 250 255

Leu Gln Asn Asp Pro Pro Thr Leu Glu Thr Gly Val Glu Asp Lys Glu
260 265 270

Met Met Lys Lys Tyr Gly Lys Ser Phe Arg Lys Leu Leu Ser Leu Cys
275 280 285

Leu Gln Lys Asp Pro Ser Lys Arg Pro Thr Ala Ala Glu Leu Leu Lys
290 295 300

Cys Lys Phe Phe Gln Lys Ala Lys Asn Arg Glu Tyr Leu Ile Glu Lys
305 310 315 320

Leu Leu Thr Arg Thr Pro Asp Ile Ala Gln Arg Ala Lys Lys Val Arg
325 330 335

Arg Val Pro Gly Ser Ser Gly His Leu His Lys Thr Glu Asp Gly Asp
340 345 350

Trp Glu Trp Ser Asp Asp Glu Met Asp Glu Lys Ser Glu Glu Gly Lys
355 360 365

Ala Ala Phe Ser Gln Glu Lys Ser Arg Arg Val Lys Glu Glu Asn Pro
370 375 380

Glu Ile Ala Val Ser Ala Ser Thr Ile Pro Glu Gln Ile Gln Ser Leu
385 390 395 400

Ser Val His Asp Ser Gln Gly Pro Pro Asn Ala Asn Glu Asp Tyr Arg
405 410 415

Glu Ala Ser Ser Cys Ala Val Asn Leu Val Leu Arg Leu Arg Asn Ser
420 425 430

Arg Lys Glu Leu Asn Asp Ile Arg Phe Glu Phe Thr Pro Gly Arg Asp
435 440 445

Thr Ala Asp Gly Val Ser Gln Glu Leu Phe Ser Ala Gly Leu Val Asp
450 455 460

Gly His Asp Val Val Ile Val Ala Ala Asn Leu Gln Lys Ile Val Asp

465 470 475 480

Asp Pro Lys Ala Leu Lys Thr Leu Thr Phe Lys Leu Ala Ser Gly Cys
485 490 495

Asp Gly Ser Glu Ile Pro Asp Glu Val Lys Leu Ile Gly Phe Ala Gln
500 505 510

Leu Ser Val Ser
515

<210> 7
<211> 414
<212> PRT
<213> Mammalian (Human) STLK4

<220>
<223> "Xaa" stands for any amino acid.

<400> 7

Lys Ser Gly Val Leu Asp Xaa Ser Thr Ile Ala Thr Ile Leu Arg Glu
1 5 10 15

Val Leu Glu Gly Leu Glu Tyr Leu His Lys Xaa Gly Gln Ile His Arg
20 25 30

Asp Val Lys Ala Gly Asn Ile Leu Xaa Gly Glu Asp Gly Ser Val Gln
35 40 45

Ile Ala Asp Phe Gly Val Ser Ala Phe Leu Ala Thr Gly Gly Asp Ile
50 55 60

Thr Arg Asn Lys Val Arg Lys Thr Phe Val Gly Thr Pro Cys Trp Met
65 70 75 80

Ala Pro Glu Val Met Glu Gln Val Arg Gly Tyr Asp Phe Lys Ala Asp
85 90 95

Ile Trp Ser Phe Gly Ile Thr Ala Ile Glu Leu Ala Thr Gly Ala Ala
100 105 110

Pro Tyr His Lys Tyr Pro Pro Met Lys Val Leu Met Leu Thr Leu Gln
115 120 125

Asn Asp Pro Pro Ser Leu Glu Thr Gly Val Gln Asp Lys Glu Met Leu
130 135 140

Lys Lys Tyr Gly Lys Ser Phe Arg Lys Met Ile Ser Leu Cys Leu Gln
145 150 155 160

Lys Asp Pro Glu Lys Arg Pro Thr Ala Ala Glu Leu Leu Arg His Lys
165 170 175

Phe Phe Gln Lys Ala Lys Asn Lys Glu Phe Leu Gln Glu Lys Thr Leu
180 185 190

Gln Arg Ala Pro Thr Ile Ser Glu Arg Ala Lys Lys Val Arg Arg Val
195 200 205

Pro Gly Ser Ser Gly Arg Leu His Lys Thr Glu Asp Gly Gly Trp Glu
210 215 220

Trp Ser Asp Asp Glu Phe Asp Glu Glu Ser Glu Glu Gly Lys Ala Ala
225 230 235 240

Ile Ser Gln Leu Arg Ser Pro Arg Val Lys Glu Ser Ile Ser Asn Ser
245 250 255

Glu Leu Phe Pro Thr Thr Asp Pro Val Gly Thr Leu Leu Gln Val Pro
260 265 270

Glu Gln Ile Ser Ala His Leu Pro Gln Pro Ala Gly Gln Ile Ala Thr
275 280 285

Gln Pro Thr Gln Val Ser Leu Pro Pro Thr Ala Glu Pro Ala Lys Thr
290 295 300

Ala Gln Ala Leu Ser Ser Gly Ser Gly Ser Gln Glu Thr Lys Ile Pro
305 310 315 320

Ile Ser Leu Val Leu Arg Leu Arg Asn Ser Lys Lys Glu Leu Asn Asp
325 330 335

Ile Arg Phe Glu Phe Thr Pro Gly Arg Asp Thr Ala Glu Gly Val Ser
340 345 350

Gln Glu Leu Ile Ser Ala Gly Leu Val Asp Gly Arg Asp Leu Val Ile
355 360 365

Val Ala Ala Asn Leu Gln Lys Ile Val Glu Glu Pro Gln Ser Asn Arg
370 375 380

Ser Val Thr Phe Lys Leu Ala Ser Gly Val Glu Gly Ser Asp Ile Pro
385 390 395 400

Asp Asp Gly Lys Leu Ile Gly Phe Ala Gln Leu Ser Ile Ser
405 410

<210> 8
<211> 274
<212> PRT
<213> Mammalian (Human) STLK5

<400> 8

Leu Ile Cys Thr His Phe Met Asp Gly Met Asn Glu Leu Ala Ile Ala
1 5 10 15

Tyr Ile Leu Gln Gly Val Leu Lys Ala Leu Asp Tyr Ile His His Met
20 25 30

Gly Tyr Val His Arg Ser Val Lys Ala Ser His Ile Leu Ile Ser Val
35 40 45

Asp Gly Lys Val Tyr Leu Ser Gly Leu Arg Ser Asn Leu Ser Met Ile
50 55 60

Ser His Gly Gln Arg Gln Arg Val Val His Asp Phe Pro Lys Tyr Ser
65 70 75 80

Val Lys Val Leu Pro Trp Leu Ser Pro Glu Val Leu Gln Gln Asn Leu
85 90 95

Gln Gly Tyr Asp Ala Lys Ser Asp Ile Tyr Ser Val Gly Ile Thr Ala
100 105 110

Cys Glu Leu Ala Asn Gly His Val Pro Phe Lys Asp Met Pro Ala Thr
115 120 125

Gln Met Leu Leu Glu Lys Leu Asn Gly Thr Val Pro Cys Leu Leu Asp
130 135 140

Thr Ser Thr Ile Pro Ala Glu Glu Leu Thr Met Ser Pro Ser Arg Ser
145 150 155 160

Val Ala Asn Ser Gly Leu Ser Asp Ser Leu Thr Thr Ser Thr Pro Arg
165 170 175

Pro Ser Asn Gly Asp Ser Pro Ser His Pro Tyr His Arg Thr Phe Ser
180 185 190

Pro His Phe His His Phe Val Glu Gln Cys Leu Gln Arg Asn Pro Asp
195 200 205

Ala Arg Pro Ser Ala Ser Thr Leu Leu Asn His Ser Phe Phe Lys Gln
210 215 220

Ile Lys Arg Arg Ala Ser Glu Ala Leu Pro Glu Leu Leu Arg Pro Val
225 230 235 240

Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser Gln Asp His Ser Gly
245 250 255

Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Leu Glu Val Asp Asp Trp
260 265 270

Glu Phe

<210> 9
<211> 3798
<212> DNA

<213> Mammalian (Human) ZC1

<400> 9

```
gagaccatgg cgaacgactc tcccgcgaaa agtctggtgg acatcgacct ctcctccctg      60
cgggatcctg ctgggatttt tgagctggtg gaagtggttg gaaatggcac ctatggacaa     120
gtctataagg gtcgacatgt taaaacgggt cagttggcag ccatcaaagt tatggatgtc     180
actgaggatg aagaggaaga aatcaaactg gagataaata tgctaaagaa atactctcat     240
cacagaaaca ttgcaacata ttatggtgct ttcatcaaaa agagccctcc aggacatgat     300
gaccaactct ggcttgttat ggagttctgt ggggctgggt ccattacaga ccttgtgaag     360
aacaccaaag ggaacacact caaagaagac tggatcgctt acatctccag agaaatcctg     420
aggggactgg cacatcttca cattcatcat gtgattcacc gggatatcaa gggccagaat     480
gtgttgctga ctgagaatgc agaggtgaaa cttgttgact ttggtgtgag tgctcagctg     540
gacaggactg tggggcggag aaatacgttc ataggcactc cctactggat ggctcctgag     600
gtcatcgcct gtgatgagaa cccagatgcc acctatgatt acagaagtga tctttggtct     660
tgtggcatta cagccattga gatggcagaa ggtgctcccc ctctctgtga catgcatcca     720
atgagagcac tgtttctcat tcccagaaac cctcctcccc ggctgaagtc aaaaaaatgg     780
tcgaagaagt tttttagttt tatagaaggg tgcctggtga agaattacat gcagcggccc     840
tctacagagc agcttttgaa acatcctttt ataaggatc agccaaatga aaggcaagtt      900
agaatccagc ttaaggatca tatagatcgt accaggaaga agagaggcga gaaagatgaa     960
actgagtatg agtacagtgg gagtgaggaa gaagaggagg aagtgcctga acaggaagga    1020
gagccaagtt ccattgtgaa cgtgcctggt gagtctactc ttcgccgaga tttcctgaga    1080
ctgcagcagg agaacaagga acgttccgag gctcttcgga gacaacagtt actacaggag    1140
caacagctcc gggagcagga agaatataaa aggcaactgc tggcagagag acagaagcgg    1200
attgagcagc agaaagaaca gaggcgacgg ctagaagagc aacaaaggag agagcgggaa    1260
gctagaaggc agcaggaacg tgaacagcga aggagagaac aagaagaaaa gaggcgtcta    1320
gaggagttgg agagaaggcg caaagaagaa gaggagagga gacgggcaga agaagaaaag    1380
aggagagttg aaagagaaca ggagtatatc aggcgacagc tagaagagga gcagcggcac    1440
ttggaagtcc ttcagcagca gctgctccag gagcaggcca tgttactgga gtgccgatgg    1500
cgggagatgg aggagcaccg gcaggcagag aggctccaga ggcagttgca acaagaacaa    1560
gcatatctcc tgtctctaca gcatgaccat aggaggccgc acccgcagca ctcgcagcag    1620
ccgccaccac cgcagcagga aaggagcaag ccaagcttcc atgctcccga gcccaaagcc    1680
cactacgagc ctgctgaccg agcgcgagag gtggaagata gatttaggaa aactaaccac    1740
agctcccctg aagcccagtc taagcagaca ggcagagtat tggagccacc agtgccttcc    1800
cgatcagagt ctttttccaa tggcaactcc gagtctgtgc atcccgccct gcagagacca    1860
gcggagccac aggttcctgt gagaacaaca tctcgctccc ctgttctgtc ccgtcgagat    1920
tccccactgc agggcagtgg gcagcagaat agccaggcag gacagagaaa ctccaccagt    1980
attgagccca ggcttctgtg ggagagagtg gagaagctgg tgcccagacc tggcagtggc    2040
agctcctcag ggtccagcaa ctcaggatcc cagcccgggt ctcaccctgg gtctcagagt    2100
ggctccgggg aacgcttcag agtgagatca tcatccaagt ctgaaggctc tccatctcag    2160
cgcctggaaa atgcagtgaa aaaacctgaa gataaaaagg aagttttcag acccctcaag    2220
cctgctgatc tgaccgcact ggccaaagag cttcgagcag tggaagatgt acggccacct    2280
cacaaagtaa cggactactc ctcatccagt gaggagtcgg ggacgacgga tgaggaggac    2340
gacgatgtgg agcaggaagg ggctgacgag tccacctcag gaccagagga caccagagca    2400
gcgtcatctc tgaatttgag caatggtgaa acggaatctg tgaaaaccat gattgtccat    2460
gatgatgtag aaagtgagcc ggccatgacc ccatccaagg agggcactct aatcgtccgc    2520
cggactcagt ccgctagtag cacactccag aaacacaaat cttcctcctc ctttacacct    2580
tttatagacc ccagattact acagatttct ccatctagcg gaacaacagt gacatctgtg    2640
gtgggatttt cctgtgatgg gatgagacca gaagccataa ggcaagatcc tacccggaaa    2700
ggctcagtgg tcaatgtgaa tcctaccaac actaggccac agagtgacac cccggagatt    2760
cgtaaataca agaagaggtt taactctgag attctgtgtg ctgccttatg ggagtgaat     2820
ttgctagtgg gtacagagag tggcctgatg ctgctggaca gaagtggcca agggaaggtc    2880
tatcctctta tcaaccgaag acgatttcaa caaatggacg tacttgaggg cttgaatgtc    2940
ttggtgacaa tatctggcaa aaaggataag ttacgtgtct actatttgtc ctggttaaga    3000
aataaaatac ttcacaatga tccagaagtt gagaagaagc agggatggac aaccgtaggg    3060
gatttggaag gatgtgtaca ttataaagtt gtaaaatatg aaagaatcaa atttctggtg    3120
```

attgctttga agagttctgt ggaagtctat gcgtgggcac caaagccata tcacaaattt 3180
atggccttta agtcatttgg agaattggta cataagccat tactggtgga tctcactgtt 3240
gaggaaggcc agaggttgaa agtgatctat ggatcctgtg ctggattcca tgctgttgat 3300
gtggattcag gatcagtcta tgacatttat ctaccaacac atatccagtg tagcatcaaa 3360
ccccatgcaa tcatcatcct ccccaataca gatggaatgg agcttctggt gtgctatgaa 3420
gatgaggggg tttatgtaaa cacatatgga aggatcacca aggatgtagt tctacagtgg 3480
ggagagatgc ctacatcagt agcatatatt cgatccaatc agacaatggg ctggggagag 3540
aaggccatag agatccgatc tgtggaaact ggtcacttgg atggtgtgtt catgcacaaa 3600
agggctcaaa gactaaaatt cttgtgtgaa cgcaatgaca aggtgttctt tgcctctgtt 3660
cggtctggtg gcagcagtca ggtttatttc atgaccttag gcaggacttc tcttctgagc 3720
tggtagaagc agtgtgatcc agggattact ggcctccaga gtcttcaaga tcctgagaac 3780
ttggaattcc ttgtaact 3798

<210> 10
<211> 4055
<212> DNA
<213> Mammalian (Human) ZC2

<400> 10

gctttcgggg aggtctatga gggtcgtcat gtcaaaacgg gccagcttgc agccatcaag 60
gttatggatg tcacagggga tgaagaggaa gaaatcaaac aagaaattaa catgttgaag 120
aaatattctc atcaccggaa tattgctaca tactatggtg cttttatcaa aaagaaccca 180
ccaggcatgg atgaccaact ttggttggtg atggagtttt gtggtgctgg ctctgtcacc 240
gacctgatca agaacacaaa aggtaacacg ttgaaagagg agtggattgc atacatctgc 300
agggaaatct tacgggggct gagtcacctg caccagcata aagtgattca tcgagatatt 360
aaagggcaaa atgtcttgct gactgaaaat gcagaagtta aactagtgga ctttggagtc 420
agtgctcagc ttgatcgaac agtgggcagg aggaatactt tcattggaac tccctactgg 480
atggcaccag aagttattgc ctgtgatgaa aacccagatg ccacatatga tttcaagagt 540
gacttgtggt ctttgggtat caccgccatt gaaatggcag aaggtgctcc ccctctctgt 600
gacatgcacc ccatgagagc tctcttcctc atcccccgga atccagcgcc tcggctgaag 660
tctaagaagt ggtcaaaaaa attccagtca tttattgaga gctgcttggt aaagaatcac 720
agccagcgac cagcaacaga acaattgatg aagcatccat ttatacgaga ccaacctaat 780
gagcgacagg tccgcattca actcaaggac catattgata gaacaaagaa gaagcgagga 840
gaaaaagatg agacagagta tgagtacagt ggaagtgagg aagaagagga ggagaatgac 900
tcaggagagc ccagctccat cctgaatctg ccaagggagt cgacgctgcg gagggacttt 960
ctgaggctgc agctggccaa caaggagcgt tctgaggccc tacggaggca gcagctggag 1020
cagcagcagc gggagaatga ggagcacaag cggcagctgc tggccgagcg tcagaagcgc 1080
atcgaggagc agaaagagca gaggcggcgg ctggaggagc aacaaaggcg agagaaggag 1140
ctgcggaagc agcaggagag ggagcagcgc cggcactatg aggagcagat gcgccgggag 1200
gaggagagga ggcgtgcgga gcatgaacag gaatataagc gcaaacaatt ggaagaacag 1260
agacaagcag aaagactgca gaggcagcta aagcaagaaa gagactactt agtttccctt 1320
cagcatcagc ggcaggagca gaggcctgtg gagaagaagc cactgtacca ttacaaagaa 1380
ggaatgagtc ctagtgagaa gccagcatgg gccaaggagg tagaagaacg gtcaaggctc 1440
aaccggcaaa gttcccctgc catgcctcac aaggttgcca acaggatatc tgaccccaac 1500
ctgcccccaa ggtcggagtc cttcagcatt agtggagttc agcctgctcg aacacccccc 1560
atgctcagac cagtcgatcc ccagatccca catctggtag ctgtaaaatc ccagggacct 1620
gccttgaccg cctcccagtc agtgcacgag cagcccacaa agggcctctc tgggtttcag 1680
gaggctctga acgtgacctc ccaccgcgtg gagatgccac gccagaactc agatcccacc 1740
tcggaaaatc ctcctctccc cactcgcatt gaaaagtttg accgaagctc ttggttacga 1800
caggaagaag acattccacc aaaggtgcct caaagaacaa cttctatatc cccagcatta 1860
gccagaaaga attctcctgg gaatggtagt gctctgggac ccagactagg atctcaaccc 1920
atcagagcaa gcaaccctga tctccggaga actgagccca tcttggagag ccccttgcag 1980
aggaccagca gtggcagttc ctccagctcc agcaccccta gctcccagcc cagctcccaa 2040

ggaggctccc agcctggatc acaagcagga tccagtgaac gcaccagagt tcgagccaac 2100
agtaagtcag aaggatcacc tgtgctcccc catgagcctg ccaaggtgaa accagaagaa 2160
tccagggaca ttacccggcc cagtcgacca gctagctaca aaaaagctat agatgaggat 2220
ctgacggcat tagccaaaga actaagagaa ctccggattg aagaaacaaa ccgcccaatg 2280
aagaaggtga ctgattactc ctcctccagt gaggagtcag aaagtagcga ggaagaggag 2340
gaagatggag agagcgagac ccatgatggg acagtggctg tcagcgacat acccagactg 2400
ataccaacag gagctccagg cagcaacgag cagtacaatg tgggaatggt ggggacgcat 2460
gggctggaga cctctcatgc ggacagtttc agcggcagta tttcaagaga aggaaccttg 2520
atgattagag agacgtctgg agagaagaag cgatctggcc acagtgacag caatggcttt 2580
gctggccaca tcaacctccc tgacctggtg cagcagagcc attctccagc tggaaccccg 2640
actgagggac tggggcgcgt ctcaacccat tcccaggaga tggactctgg gactgaatat 2700
ggcatgggga gcagcaccaa agcctccttc accccctttg tggaccccag agtataccag 2760
acgtctccca ctgatgaaga tgaagaggat gaggaatcat cagccgcagc tctgtttact 2820
ggcgaacttc ttaggcaaga acaggccaaa ctcaatgaag caagaaagat ttcggtggta 2880
aatgtaaacc caaccaacat tcggcctcat agcgacacac cagaaatcag aaaatacaag 2940
aaacgattca actcagaaat actttgtgca gctctgtggg gtgtaaacct tctggtgggg 3000
actgaaaatg gcctgatgct tttggaccga agtgggcaag gcaaagtcta taatctgatc 3060
aaccggaggc gatttcagca gatggatgtg ctagagggac tgaatgtcct tgtgacaatt 3120
tcaggaaaga agaataagct acgagtttac tatctttcat ggttaagaaa cagaatacta 3180
cataatgacc cagaagtaga aaagaaacaa ggctggatca ctgttgggga cttggaaggc 3240
tgtatacatt ataaagttgt taaatatgaa aggatcaaat ttttggtgat tgccttaaag 3300
aatgctgtgg aaatatatgc ttgggctcct aaaccgtatc ataaattcat ggcatttaag 3360
tcttttgcag atctccagca caagcctctg ctagttgatc tcacggtaga agaaggtcaa 3420
agattaaagg ttatttttgg ttcacacact ggtttccatg taattgatgt tgattcagga 3480
aactcttatg atatctacac accatctcat attcagggca atatcactcc tcatgctatt 3540
gtcatcttgc ctaaaacaga tggaatggaa atgcttgttt gctatgagga tgagggggtg 3600
tatgtaaaca cctatggccg gataactaag gatgtggtgc tccaatgggg agaaatgccc 3660
acgtctgtgg cctacattca ttccaatcag ataatgggct ggggcgagaa agctattgag 3720
atccggtcag tggaaacagg acatttggat ggagtattta tgcataagcg agctcaaagg 3780
ttaaagtttc tatgtgaaag aaatgataag gtattttttg catccgtgcg atctggagga 3840
agtagccaag tgtttttcat gaccctcaac agaaattcca tgatgaactg gtaacagaag 3900
agcacttggc acttatcttc atggcgttat ttctaattta aagaacata actcatgtgg 3960
acttatgcca gtctagaggc agaatcagaa ggcttggttg aacatatcgc tttccctttt 4020
tcctctccct ccgcccctcc cagtacagtc catct 4055

<210> 11
<211> 4133
<212> DNA
<213> Mammalian (Human) ZC3

<400> 11

gcatttgggg aggtgtatga gggtcggcat gtcaagacgg ggcagctggc tgccatcaag 60
gtcatggatg tcacggagga cgaggaggaa gagatcaaac aggagatcaa catgctgaaa 120
aagtactctc accaccgcaa catcgccacc tactacggag ccttcatcaa gaagagcccc 180
ccgggaaacg atgaccagct ctggctggtg atggagttct gtggtgctgg ttcagtgact 240
gacctggtaa agaacacaaa aggcaacgcc ctgaaggagg actgtatcgc ctatatctgc 300
agggagatcc tcaggggtct ggcccatctc catgcccaca aggtgatcca tcgagacatc 360
aaggggcaga atgtgctgct gacagagaat gctgaggtca agctagtgga ttttggggtg 420
agtgctcagc tggaccgcac cgtgggcaga cggaacactt tcattgggac tccctactgg 480
atggctccag aggtcatcgc ctgtgatgag aaccctgatg ccacctatga ttacaggagt 540
gatatttggt ctctaggaat cacagccatc gagatggcag agggagcccc ccctctgtgt 600
gacatgcacc ccatgcgagc cctcttcctc attcctcgga accctccgcc caggctcaag 660
tccaagaagt ggtctaagaa gttcattgac ttcattgaca catgtctcat caagacttac 720

```
ctgagccgcc cacccacgga gcagctactg aagtttccct tcatccggga ccagcccacg     780
gagcggcagg tccgcatcca gcttaaggac cacattgacc gatcccggaa gaagcggggt     840
gagaaagagg agacagaata tgagtacagc ggcagcgagg aggaagatga cagccatgga     900
gaggaaggag agccaagctc catcatgaac gtgcctggag agtcgactct acgccgggag     960
tttctccggc tccagcagga aaataagagc aactcagagg ctttaaaaca gcagcagcag    1020
ctgcagcagc agcagcagcg agaccccgag gcacacatca aacacctgct gcaccagcgg    1080
cagcggcgca tagaggagca gaaggaggag cggcgccgcg tggaggagca acagcggcgg    1140
gagcgggagc agcggaagct gcaggagaag gagcagcagc ggcggctgga ggacatgcag    1200
gctctgcggc gggaggagga gcggcggcag gcggagcgcg agcaggaata tattcgtcac    1260
aggctagagg aggagcagcg acagctcgag atccttcagc aacagctgct ccaggaacag    1320
gccctgctgc tggaatacaa gcggaagcag ctggaggagc agcggcagtc agaacgtctc    1380
cagaggcagc tgcagcagga gcatgcctac ctcaagtccc tgcagcagca gcaacagcag    1440
cagcagcttc agaaacaaca gcagcagcag ctcctgcctg gggacaggaa gcccctgtac    1500
cattatggtc ggggcatgaa tcccgctgac aaaccagcct gggcccgaga ggtagaagag    1560
agaacaagga tgaacaagca gcagaactct cccttggcca agagcaagcc aggcagcacg    1620
gggcctgagc cccccatccc ccaggcctcc ccagggcccc caggacccct ttcccagact    1680
cctcctatgc agaggccggt ggagccccag gagggaccgc acaagagcct ggtggcacac    1740
cgggtcccac tgaagccata tgcagcacct gtaccccgat cccagtccct gcaggaccag    1800
cccacccgaa acctggctgc cttcccagcc tcccatgacc ccgaccctgc catccccgca    1860
cccactgcca cgcccagtgc ccgaggagct gtcatccgcc agaattcaga ccccacctct    1920
gaaggacctg gccccagccc gaatcccccca gcctgggtcc gcccagataa cgaggcccca    1980
cccaaggtgc ctcagaggac ctcatctatc gccactgccc ttaacaccag tggggccgga    2040
gggtcccggc cagcccaggc agtccgtgcc agacctcgca gcaactccgc ctggcaaatc    2100
tatctgcaaa ggcgggcaga gcggggcacc ccaaagcctc cagggccccc tgctcagccc    2160
cctggcccgc ccaacgcctc tagtaacccc gacctcagga ggagcgaccc tggctgggaa    2220
cgctcggaca gcgtccttcc agcctctcac gggcacctcc cccaggctgg ctcactggag    2280
cggaaccgcg tgggagtctc ctccaaaccg gacagctccc ctgtgctctc ccctgggaat    2340
aaagccaagc ccgacgacca ccgctcacgg ccaggccggc ccgcagactt tgtgttgctg    2400
aaagagcgga ctctggacga ggcccctcgg cctcccaaga aggccatgga ctactcgtcg    2460
tccagcgagg aggtggaaag cagtgaggac gacgaggagg aaggcgaagg cgggccagca    2520
gaggggagca gagatacccc tggggggccgc gatggggata cagacagcgt cagcaccatg    2580
gtggtccacg acgtcgagga gatcaccggg acccagcccc catacggggg cggcaccatg    2640
gtggtccagc gcacccctga agaggagcgg aacctgctgc atgctgacag caatgggtac    2700
acaaacctgc ctgacgtggt ccagcccagc cactcaccca ccgagaacag caaaggccaa    2760
agcccacccct cgaaggatgg gagtggtgac taccagtctc gtgggctggt aaaggcccct    2820
ggcaagagct cgttcacgat gtttgtggat ctagggatct accagcctgg aggcagtggg    2880
gacagcatcc ccatcacagc cctagtgggt ggagagggca ctcggctcga ccagctgcag    2940
tacgacgtga ggaagggttc tgtggtcaac gtgaatccca ccaacacccg ggcccacagt    3000
gagacccctg agatccggaa gtacaagaag cgattcaact ccgagatcct ctgtgcagcc    3060
ctttgggggg tcaacctgct ggtgggcacg gagaacgggc tgatgttgct ggaccgaagt    3120
gggcagggca aggtgtatgg actcattggg cggcgacgct tccagcagat ggatgtgctg    3180
gaggggctca acctgctcat caccatctca gggaaaagga acaaactgcg ggtgtattac    3240
ttgtcctggc tccggaacaa gattctgcac aatgacccag aagtggagaa gaagcagggc    3300
tggaccaccg tgggggacat ggagggctgc gggcactacc gtgttgtgaa atacgagcgg    3360
attaagttcc tggtcatcgc cctcaagagc tccgtggagg tgtatgcctg ggcccccaaa    3420
ccctaccaca aattcatggc cttcaagtcc tttgccgacc tcccccaccg ccctctgctg    3480
gtcgacctga cagtagagga ggggcagcgg ctcaaggtca tctatggctc cagtgctggc    3540
ttccatgctg tggatgtcga ctcggggaac agctatgaca tctacatccc tgtgcacatc    3600
cagagccaga tcacgcccca tgccatcatc ttcctcccca acaccgacgg catggagatg    3660
ctgctgtgct acgaggacga gggtgtctac gtcaacacgt acgggcgcat cattaaggat    3720
gtggtgctgc agtgggggga gatgcctact tctgtggcct acatctgctc caaccagata    3780
atgggctggg gtgagaaagc cattgagatc cgctctgtgg agacgggcca cctcgacggg    3840
gtcttcatgc acaaacgagc tcagaggctc aagttcctgt gtgagcggaa tgacaaggtg    3900
ttttttgcct cagtccgctc tgggggcagc agccaagttt acttcatgac tctgaaccgt    3960
aaccgcatca tgaactggtg acggggccct gggctggggc tgtcccacac tggacccagc    4020
tctccccctg cagccaggct tcccgggccg cccctctttc ccctccctgg gcttttgctt    4080
```

ttactggttt gatttcactg gagcctgctg ggaacgtgac ctctgacccc tga 4133

<210> 12
<211> 1459
<212> DNA
<213> Mammalian (Human) ZC4

<400> 12

caatgttaac ccactctatg tctctcctgc atgtaaaaaa ccactaatcc acatgtatga 60
aaaggagttc acttctgaga tctgctgtgg ttctttgtgg ggagtcaatt tgctgttggg 120
aaccccgatct aatctatatc tgatggacag aagtggaaag gctgacatta ctaaacttat 180
aaggcgaaga ccattccgcc agattcaagt cttagagcca ctcaatttgc tgattaccat 240
ctcaggtcat aagaacagac ttcgggtgta tcatctgacc tggttgagga acaagatttt 300
gaataatgat ccagaaagta aaagaaggca agaagaaatg ctgaagacag aggaagcctg 360
caaagctatt gataagttaa caggctgtga acacttcagt gtcctccaac atgaagaaac 420
aacatatatt gcaattgctt tgaaatcatc aattcacctt tatgcatggg caccaaagtc 480
ctttgatgaa agcactgcta ttaaagtatt tccaacactt gatcataagc cagtgacagt 540
tgacctggct attggttctg aaaaaagact aaagattttc ttcagctcag cagatggata 600
tcacctcatc gatgcagaat ctgaggttat gtctgatgtg accctgccaa agaatcccct 660
ggaaatcatt ataccacaga atatcatcat tttacctgat tgcttgggaa ttggcatgat 720
gctcaccttc aatgctgaag ccctctctgt ggaagcaaat gaacaactct tcaagaagat 780
ccttgaaatg tggaaagaca taccatcttc tatagctttt gaatgtacac agcgaaccac 840
aggatggggc caaaaggcca ttgaagtgcg ctctttgcaa tccagggttc tggaaagtga 900
gctgaagcgc aggtcaatta agaagctgag attcctgtgc acccggggtg acaagctgtt 960
ctttacctct accctgcgca atcaccacag ccgggtttac ttcatgacac ttggaaaact 1020
tgaagagctc caaagcaatt atgatgtcta aaagtttcca gtgatttatt accacattat 1080
aaacatcatg tataggcagt ctgcatcttc agatttcaga gattaaatga gtattcagtt 1140
ttatttttag taaagattaa atccaaaact ttacttttaa tgtagcacag aatagtttta 1200
atgagaaatg cagctttatg tataaaatta actatagcaa gctctaggta ctccaatggt 1260
gtacaatgtc ttttgcacaa actttgtaac ttttgttact gtgaattcaa acattactct 1320
ttggacagtt tggacagtat ctgtattcag attttacaac atggagtaaa gaaacctgtt 1380
atgaattaga ttacaagcag ccttcaaaag aattggcact gggataagat ttttcagaaa 1440
agaaaaacat cggcaaact 1459

<210> 13
<211> 1239
<212> PRT
<213> Mammalian (Human) ZC1

<400> 13

Met Ala Asn Asp Ser Pro Ala Lys Ser Leu Val Asp Ile Asp Leu Ser
1 5 10 15

Ser Leu Arg Asp Pro Ala Gly Ile Phe Glu Leu Val Glu Val Val Gly
20 25 30

Asn Gly Thr Tyr Gly Gln Val Tyr Lys Gly Arg His Val Lys Thr Gly

35 40 45

Gln Leu Ala Ala Ile Lys Val Met Asp Val Thr Glu Asp Glu Glu Glu
50 55 60

Glu Ile Lys Leu Glu Ile Asn Met Leu Lys Lys Tyr Ser His His Arg
65 70 75 80

Asn Ile Ala Thr Tyr Tyr Gly Ala Phe Ile Lys Lys Ser Pro Pro Gly
85 90 95

His Asp Asp Gln Leu Trp Leu Val Met Glu Phe Cys Gly Ala Gly Ser
100 105 110

Ile Thr Asp Leu Val Lys Asn Thr Lys Gly Asn Thr Leu Lys Glu Asp
115 120 125

Trp Ile Ala Tyr Ile Ser Arg Glu Ile Leu Arg Gly Leu Ala His Leu
130 135 140

His Ile His His Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu
145 150 155 160

Leu Thr Glu Asn Ala Glu Val Lys Leu Val Asp Phe Gly Val Ser Ala
165 170 175

Gln Leu Asp Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro
180 185 190

Tyr Trp Met Ala Pro Glu Val Ile Ala Cys Asp Glu Asn Pro Asp Ala
195 200 205

Thr Tyr Asp Tyr Arg Ser Asp Leu Trp Ser Cys Gly Ile Thr Ala Ile
210 215 220

Glu Met Ala Glu Gly Ala Pro Pro Leu Cys Asp Met His Pro Met Arg
225 230 235 240

Ala Leu Phe Leu Ile Pro Arg Asn Pro Pro Pro Arg Leu Lys Ser Lys
245 250 255

Lys Trp Ser Lys Lys Phe Phe Ser Phe Ile Glu Gly Cys Leu Val Lys
260 265 270

Asn Tyr Met Gln Arg Pro Ser Thr Glu Gln Leu Leu Lys His Pro Phe
275 280 285

Ile Arg Asp Gln Pro Asn Glu Arg Gln Val Arg Ile Gln Leu Lys Asp
290 295 300

His Ile Asp Arg Thr Arg Lys Lys Arg Gly Glu Lys Asp Glu Thr Glu
305 310 315 320

Tyr Glu Tyr Ser Gly Ser Glu Glu Glu Glu Glu Glu Val Pro Glu Gln
325 330 335

```
Glu Gly Glu Pro Ser Ser Ile Val Asn Val Pro Gly Glu Ser Thr Leu
            340                 345                 350

Arg Arg Asp Phe Leu Arg Leu Gln Gln Glu Asn Lys Glu Arg Ser Glu
        355                 360                 365

Ala Leu Arg Arg Gln Gln Leu Leu Gln Glu Gln Gln Leu Arg Glu Gln
    370                 375                 380

Glu Glu Tyr Lys Arg Gln Leu Leu Ala Glu Arg Gln Lys Arg Ile Glu
385                 390                 395                 400

Gln Gln Lys Glu Gln Arg Arg Arg Leu Glu Glu Gln Gln Arg Arg Glu
                405                 410                 415

Arg Glu Ala Arg Arg Gln Gln Glu Arg Glu Gln Arg Arg Arg Glu Gln
            420                 425                 430

Glu Glu Lys Arg Arg Leu Glu Glu Leu Glu Arg Arg Arg Lys Glu Glu
        435                 440                 445

Glu Glu Arg Arg Arg Ala Glu Glu Glu Lys Arg Arg Val Glu Arg Glu
    450                 455                 460

Gln Glu Tyr Ile Arg Arg Gln Leu Glu Glu Glu Gln Arg His Leu Glu
465                 470                 475                 480

Val Leu Gln Gln Gln Leu Leu Gln Glu Gln Ala Met Leu Leu Glu Cys
                485                 490                 495

Arg Trp Arg Glu Met Glu Glu His Arg Gln Ala Glu Arg Leu Gln Arg
            500                 505                 510

Gln Leu Gln Gln Glu Gln Ala Tyr Leu Leu Ser Leu Gln His Asp His
        515                 520                 525

Arg Arg Pro His Pro Gln His Ser Gln Gln Pro Pro Pro Pro Gln Gln
    530                 535                 540

Glu Arg Ser Lys Pro Ser Phe His Ala Pro Glu Pro Lys Ala His Tyr
545                 550                 555                 560

Glu Pro Ala Asp Arg Ala Arg Glu Val Glu Asp Arg Phe Arg Lys Thr
                565                 570                 575

Asn His Ser Ser Pro Glu Ala Gln Ser Lys Gln Thr Gly Arg Val Leu
            580                 585                 590

Glu Pro Pro Val Pro Ser Arg Ser Glu Ser Phe Ser Asn Gly Asn Ser
        595                 600                 605

Glu Ser Val His Pro Ala Leu Gln Arg Pro Ala Glu Pro Gln Val Pro
    610                 615                 620

Val Arg Thr Thr Ser Arg Ser Pro Val Leu Ser Arg Arg Asp Ser Pro
```

625 630 635 640

Leu Gln Gly Ser Gly Gln Gln Asn Ser Gln Ala Gly Gln Arg Asn Ser
645 650 655

Thr Ser Ile Glu Pro Arg Leu Leu Trp Glu Arg Val Glu Lys Leu Val
660 665 670

Pro Arg Pro Gly Ser Gly Ser Ser Ser Gly Ser Ser Asn Ser Gly Ser
675 680 685

Gln Pro Gly Ser His Pro Gly Ser Gln Ser Gly Ser Gly Glu Arg Phe
690 695 700

Arg Val Arg Ser Ser Ser Lys Ser Glu Gly Ser Pro Ser Gln Arg Leu
705 710 715 720

Glu Asn Ala Val Lys Lys Pro Glu Asp Lys Lys Glu Val Phe Arg Pro
725 730 735

Leu Lys Pro Ala Asp Leu Thr Ala Leu Ala Lys Glu Leu Arg Ala Val
740 745 750

Glu Asp Val Arg Pro Pro His Lys Val Thr Asp Tyr Ser Ser Ser Ser
755 760 765

Glu Glu Ser Gly Thr Thr Asp Glu Glu Asp Asp Asp Val Glu Gln Glu
770 775 780

Gly Ala Asp Glu Ser Thr Ser Gly Pro Glu Asp Thr Arg Ala Ala Ser
785 790 795 800

Ser Leu Asn Leu Ser Asn Gly Glu Thr Glu Ser Val Lys Thr Met Ile
805 810 815

Val His Asp Asp Val Glu Ser Glu Pro Ala Met Thr Pro Ser Lys Glu
820 825 830

Gly Thr Leu Ile Val Arg Arg Thr Gln Ser Ala Ser Ser Thr Leu Gln
835 840 845

Lys His Lys Ser Ser Ser Ser Phe Thr Pro Phe Ile Asp Pro Arg Leu
850 855 860

Leu Gln Ile Ser Pro Ser Ser Gly Thr Thr Val Thr Ser Val Val Gly
865 870 875 880

Phe Ser Cys Asp Gly Met Arg Pro Glu Ala Ile Arg Gln Asp Pro Thr
885 890 895

Arg Lys Gly Ser Val Val Asn Val Asn Pro Thr Asn Thr Arg Pro Gln
900 905 910

Ser Asp Thr Pro Glu Ile Arg Lys Tyr Lys Lys Arg Phe Asn Ser Glu
915 920 925

Ile Leu Cys Ala Ala Leu Trp Gly Val Asn Leu Leu Val Gly Thr Glu
930 935 940

Ser Gly Leu Met Leu Leu Asp Arg Ser Gly Gln Gly Lys Val Tyr Pro
945 950 955 960

Leu Ile Asn Arg Arg Arg Phe Gln Gln Met Asp Val Leu Glu Gly Leu
965 970 975

Asn Val Leu Val Thr Ile Ser Gly Lys Lys Asp Lys Leu Arg Val Tyr
980 985 990

Tyr Leu Ser Trp Leu Arg Asn Lys Ile Leu His Asn Asp Pro Glu Val
995 1000 1005

Glu Lys Lys Gln Gly Trp Thr Thr Val Gly Asp Leu Glu Gly Cys Val
1010 1015 1020

His Tyr Lys Val Val Lys Tyr Glu Arg Ile Lys Phe Leu Val Ile Ala
1025 1030 1035 1040

Leu Lys Ser Ser Val Glu Val Tyr Ala Trp Ala Pro Lys Pro Tyr His
1045 1050 1055

Lys Phe Met Ala Phe Lys Ser Phe Gly Glu Leu Val His Lys Pro Leu
1060 1065 1070

Leu Val Asp Leu Thr Val Glu Glu Gly Gln Arg Leu Lys Val Ile Tyr
1075 1080 1085

Gly Ser Cys Ala Gly Phe His Ala Val Asp Val Asp Ser Gly Ser Val
1090 1095 1100

Tyr Asp Ile Tyr Leu Pro Thr His Ile Gln Cys Ser Ile Lys Pro His
1105 1110 1115 1120

Ala Ile Ile Ile Leu Pro Asn Thr Asp Gly Met Glu Leu Leu Val Cys
1125 1130 1135

Tyr Glu Asp Glu Gly Val Tyr Val Asn Thr Tyr Gly Arg Ile Thr Lys
1140 1145 1150

Asp Val Val Leu Gln Trp Gly Glu Met Pro Thr Ser Val Ala Tyr Ile
1155 1160 1165

Arg Ser Asn Gln Thr Met Gly Trp Gly Glu Lys Ala Ile Glu Ile Arg
1170 1175 1180

Ser Val Glu Thr Gly His Leu Asp Gly Val Phe Met His Lys Arg Ala
1185 1190 1195 1200

Gln Arg Leu Lys Phe Leu Cys Glu Arg Asn Asp Lys Val Phe Phe Ala
1205 1210 1215

Ser Val Arg Ser Gly Gly Ser Ser Gln Val Tyr Phe Met Thr Leu Gly
1220 1225 1230

Arg Thr Ser Leu Leu Ser Trp
1235

<210> 14
<211> 1297
<212> PRT
<213> Mammalian (Human) ZC2

<400> 14

Ala Phe Gly Glu Val Tyr Glu Gly Arg His Val Lys Thr Gly Gln Leu
1 5 10 15

Ala Ala Ile Lys Val Met Asp Val Thr Gly Asp Glu Glu Glu Glu Ile
20 25 30

Lys Gln Glu Ile Asn Met Leu Lys Lys Tyr Ser His His Arg Asn Ile
35 40 45

Ala Thr Tyr Tyr Gly Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp
50 55 60

Asp Gln Leu Trp Leu Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr
65 70 75 80

Asp Leu Ile Lys Asn Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile
85 90 95

Ala Tyr Ile Cys Arg Glu Ile Leu Arg Gly Leu Ser His Leu His Gln
100 105 110

His Lys Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu Leu Thr
115 120 125

Glu Asn Ala Glu Val Lys Leu Val Asp Phe Gly Val Ser Ala Gln Leu
130 135 140

Asp Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp
145 150 155 160

Met Ala Pro Glu Val Ile Ala Cys Asp Glu Asn Pro Asp Ala Thr Tyr
165 170 175

Asp Phe Lys Ser Asp Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met
180 185 190

Ala Glu Gly Ala Pro Pro Leu Cys Asp Met His Pro Met Arg Ala Leu
195 200 205

Phe Leu Ile Pro Arg Asn Pro Ala Pro Arg Leu Lys Ser Lys Lys Trp

210 215 220

Ser Lys Lys Phe Gln Ser Phe Ile Glu Ser Cys Leu Val Lys Asn His
225 230 235 240

Ser Gln Arg Pro Ala Thr Glu Gln Leu Met Lys His Pro Phe Ile Arg
245 250 255

Asp Gln Pro Asn Glu Arg Gln Val Arg Ile Gln Leu Lys Asp His Ile
260 265 270

Asp Arg Thr Lys Lys Lys Arg Gly Glu Lys Asp Glu Thr Glu Tyr Glu
275 280 285

Tyr Ser Gly Ser Glu Glu Glu Glu Glu Glu Asn Asp Ser Gly Glu Pro
290 295 300

Ser Ser Ile Leu Asn Leu Pro Arg Glu Ser Thr Leu Arg Arg Asp Phe
305 310 315 320

Leu Arg Leu Gln Leu Ala Asn Lys Glu Arg Ser Glu Ala Leu Arg Arg
325 330 335

Gln Gln Leu Glu Gln Gln Gln Arg Glu Asn Glu Glu His Lys Arg Gln
340 345 350

Leu Leu Ala Glu Arg Gln Lys Arg Ile Glu Glu Gln Lys Glu Gln Arg
355 360 365

Arg Arg Leu Glu Glu Gln Gln Arg Arg Glu Lys Glu Leu Arg Lys Gln
370 375 380

Gln Glu Arg Glu Gln Arg Arg His Tyr Glu Glu Gln Met Arg Arg Glu
385 390 395 400

Glu Glu Arg Arg Arg Ala Glu His Glu Gln Glu Tyr Lys Arg Lys Gln
405 410 415

Leu Glu Glu Gln Arg Gln Ala Glu Arg Leu Gln Arg Gln Leu Lys Gln
420 425 430

Glu Arg Asp Tyr Leu Val Ser Leu Gln His Gln Arg Gln Glu Gln Arg
435 440 445

Pro Val Glu Lys Lys Pro Leu Tyr His Tyr Lys Glu Gly Met Ser Pro
450 455 460

Ser Glu Lys Pro Ala Trp Ala Lys Glu Val Glu Glu Arg Ser Arg Leu
465 470 475 480

Asn Arg Gln Ser Ser Pro Ala Met Pro His Lys Val Ala Asn Arg Ile
485 490 495

Ser Asp Pro Asn Leu Pro Pro Arg Ser Glu Ser Phe Ser Ile Ser Gly
500 505 510

Val Gln Pro Ala Arg Thr Pro Pro Met Leu Arg Pro Val Asp Pro Gln
515 520 525

Ile Pro His Leu Val Ala Val Lys Ser Gln Gly Pro Ala Leu Thr Ala
530 535 540

Ser Gln Ser Val His Glu Gln Pro Thr Lys Gly Leu Ser Gly Phe Gln
545 550 555 560

Glu Ala Leu Asn Val Thr Ser His Arg Val Glu Met Pro Arg Gln Asn
565 570 575

Ser Asp Pro Thr Ser Glu Asn Pro Pro Leu Pro Thr Arg Ile Glu Lys
580 585 590

Phe Asp Arg Ser Ser Trp Leu Arg Gln Glu Glu Asp Ile Pro Pro Lys
595 600 605

Val Pro Gln Arg Thr Thr Ser Ile Ser Pro Ala Leu Ala Arg Lys Asn
610 615 620

Ser Pro Gly Asn Gly Ser Ala Leu Gly Pro Arg Leu Gly Ser Gln Pro
625 630 635 640

Ile Arg Ala Ser Asn Pro Asp Leu Arg Arg Thr Glu Pro Ile Leu Glu
645 650 655

Ser Pro Leu Gln Arg Thr Ser Ser Gly Ser Ser Ser Ser Ser Ser Thr
660 665 670

Pro Ser Ser Gln Pro Ser Ser Gln Gly Gly Ser Gln Pro Gly Ser Gln
675 680 685

Ala Gly Ser Ser Glu Arg Thr Arg Val Arg Ala Asn Ser Lys Ser Glu
690 695 700

Gly Ser Pro Val Leu Pro His Glu Pro Ala Lys Val Lys Pro Glu Glu
705 710 715 720

Ser Arg Asp Ile Thr Arg Pro Ser Arg Pro Ala Ser Tyr Lys Lys Ala
725 730 735

Ile Asp Glu Asp Leu Thr Ala Leu Ala Lys Glu Leu Arg Glu Leu Arg
740 745 750

Ile Glu Glu Thr Asn Arg Pro Met Lys Lys Val Thr Asp Tyr Ser Ser
755 760 765

Ser Ser Glu Glu Ser Glu Ser Ser Glu Glu Glu Glu Glu Asp Gly Glu
770 775 780

Ser Glu Thr His Asp Gly Thr Val Ala Val Ser Asp Ile Pro Arg Leu
785 790 795 800

Ile Pro Thr Gly Ala Pro Gly Ser Asn Glu Gln Tyr Asn Val Gly Met
805 810 815

Val Gly Thr His Gly Leu Glu Thr Ser His Ala Asp Ser Phe Ser Gly
820 825 830

Ser Ile Ser Arg Glu Gly Thr Leu Met Ile Arg Glu Thr Ser Gly Glu
835 840 845

Lys Lys Arg Ser Gly His Ser Asp Ser Asn Gly Phe Ala Gly His Ile
850 855 860

Asn Leu Pro Asp Leu Val Gln Gln Ser His Ser Pro Ala Gly Thr Pro
865 870 875 880

Thr Glu Gly Leu Gly Arg Val Ser Thr His Ser Gln Glu Met Asp Ser
885 890 895

Gly Thr Glu Tyr Gly Met Gly Ser Ser Thr Lys Ala Ser Phe Thr Pro
900 905 910

Phe Val Asp Pro Arg Val Tyr Gln Thr Ser Pro Thr Asp Glu Asp Glu
915 920 925

Glu Asp Glu Glu Ser Ser Ala Ala Ala Leu Phe Thr Gly Glu Leu Leu
930 935 940

Arg Gln Glu Gln Ala Lys Leu Asn Glu Ala Arg Lys Ile Ser Val Val
945 950 955 960

Asn Val Asn Pro Thr Asn Ile Arg Pro His Ser Asp Thr Pro Glu Ile
965 970 975

Arg Lys Tyr Lys Lys Arg Phe Asn Ser Glu Ile Leu Cys Ala Ala Leu
980 985 990

Trp Gly Val Asn Leu Leu Val Gly Thr Glu Asn Gly Leu Met Leu Leu
995 1000 1005

Asp Arg Ser Gly Gln Gly Lys Val Tyr Asn Leu Ile Asn Arg Arg Arg
1010 1015 1020

Phe Gln Gln Met Asp Val Leu Glu Gly Leu Asn Val Leu Val Thr Ile
1025 1030 1035 1040

Ser Gly Lys Lys Asn Lys Leu Arg Val Tyr Tyr Leu Ser Trp Leu Arg
1045 1050 1055

Asn Arg Ile Leu His Asn Asp Pro Glu Val Glu Lys Lys Gln Gly Trp
1060 1065 1070

Ile Thr Val Gly Asp Leu Glu Gly Cys Ile His Tyr Lys Val Val Lys
1075 1080 1085

Tyr Glu Arg Ile Lys Phe Leu Val Ile Ala Leu Lys Asn Ala Val Glu

1090 1095 1100

Ile Tyr Ala Trp Ala Pro Lys Pro Tyr His Lys Phe Met Ala Phe Lys
1105 1110 1115 1120

Ser Phe Ala Asp Leu Gln His Lys Pro Leu Leu Val Asp Leu Thr Val
1125 1130 1135

Glu Glu Gly Gln Arg Leu Lys Val Ile Phe Gly Ser His Thr Gly Phe
1140 1145 1150

His Val Ile Asp Val Asp Ser Gly Asn Ser Tyr Asp Ile Tyr Thr Pro
1155 1160 1165

Ser His Ile Gln Gly Asn Ile Thr Pro His Ala Ile Val Ile Leu Pro
1170 1175 1180

Lys Thr Asp Gly Met Glu Met Leu Val Cys Tyr Glu Asp Glu Gly Val
1185 1190 1195 1200

Tyr Val Asn Thr Tyr Gly Arg Ile Thr Lys Asp Val Val Leu Gln Trp
1205 1210 1215

Gly Glu Met Pro Thr Ser Val Ala Tyr Ile His Ser Asn Gln Ile Met
1220 1225 1230

Gly Trp Gly Glu Lys Ala Ile Glu Ile Arg Ser Val Glu Thr Gly His
1235 1240 1245

Leu Asp Gly Val Phe Met His Lys Arg Ala Gln Arg Leu Lys Phe Leu
1250 1255 1260

Cys Glu Arg Asn Asp Lys Val Phe Phe Ala Ser Val Arg Ser Gly Gly
1265 1270 1275 1280

Ser Ser Gln Val Phe Phe Met Thr Leu Asn Arg Asn Ser Met Met Asn
1285 1290 1295

Trp

<210> 15
<211> 1326
<212> PRT
<213> Mammalian (Human) ZC3

<400> 15

Ala Phe Gly Glu Val Tyr Glu Gly Arg His Val Lys Thr Gly Gln Leu
1 5 10 15

Ala Ala Ile Lys Val Met Asp Val Thr Glu Asp Glu Glu Glu Glu Ile
20 25 30

Lys Gln Glu Ile Asn Met Leu Lys Lys Tyr Ser His His Arg Asn Ile
35 40 45

Ala Thr Tyr Tyr Gly Ala Phe Ile Lys Lys Ser Pro Pro Gly Asn Asp
50 55 60

Asp Gln Leu Trp Leu Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr
65 70 75 80

Asp Leu Val Lys Asn Thr Lys Gly Asn Ala Leu Lys Glu Asp Cys Ile
85 90 95

Ala Tyr Ile Cys Arg Glu Ile Leu Arg Gly Leu Ala His Leu His Ala
100 105 110

His Lys Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu Leu Thr
115 120 125

Glu Asn Ala Glu Val Lys Leu Val Asp Phe Gly Val Ser Ala Gln Leu
130 135 140

Asp Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp
145 150 155 160

Met Ala Pro Glu Val Ile Ala Cys Asp Glu Asn Pro Asp Ala Thr Tyr
165 170 175

Asp Tyr Arg Ser Asp Ile Trp Ser Leu Gly Ile Thr Ala Ile Glu Met
180 185 190

Ala Glu Gly Ala Pro Pro Leu Cys Asp Met His Pro Met Arg Ala Leu
195 200 205

Phe Leu Ile Pro Arg Asn Pro Pro Pro Arg Leu Lys Ser Lys Lys Trp
210 215 220

Ser Lys Lys Phe Ile Asp Phe Ile Asp Thr Cys Leu Ile Lys Thr Tyr
225 230 235 240

Leu Ser Arg Pro Pro Thr Glu Gln Leu Leu Lys Phe Pro Phe Ile Arg
245 250 255

Asp Gln Pro Thr Glu Arg Gln Val Arg Ile Gln Leu Lys Asp His Ile
260 265 270

Asp Arg Ser Arg Lys Lys Arg Gly Glu Lys Glu Glu Thr Glu Tyr Glu
275 280 285

Tyr Ser Gly Ser Glu Glu Glu Asp Asp Ser His Gly Glu Glu Gly Glu
290 295 300

Pro Ser Ser Ile Met Asn Val Pro Gly Glu Ser Thr Leu Arg Arg Glu
305 310 315 320

Phe Leu Arg Leu Gln Gln Glu Asn Lys Ser Asn Ser Glu Ala Leu Lys
325 330 335

```
Gln Gln Gln Gln Leu Gln Gln Gln Gln Gln Arg Asp Pro Glu Ala His
            340                 345                 350

Ile Lys His Leu Leu His Gln Arg Gln Arg Arg Ile Glu Glu Gln Lys
        355                 360                 365

Glu Glu Arg Arg Arg Val Glu Glu Gln Gln Arg Arg Glu Arg Glu Gln
    370                 375                 380

Arg Lys Leu Gln Glu Lys Glu Gln Gln Arg Arg Leu Glu Asp Met Gln
385                 390                 395                 400

Ala Leu Arg Arg Glu Glu Glu Arg Arg Gln Ala Glu Arg Glu Gln Glu
                405                 410                 415

Tyr Ile Arg His Arg Leu Glu Glu Glu Gln Arg Gln Leu Glu Ile Leu
            420                 425                 430

Gln Gln Gln Leu Leu Gln Glu Gln Ala Leu Leu Leu Glu Tyr Lys Arg
        435                 440                 445

Lys Gln Leu Glu Glu Gln Arg Gln Ser Glu Arg Leu Gln Arg Gln Leu
    450                 455                 460

Gln Gln Glu His Ala Tyr Leu Lys Ser Leu Gln Gln Gln Gln Gln Gln
465                 470                 475                 480

Gln Gln Leu Gln Lys Gln Gln Gln Gln Gln Leu Leu Pro Gly Asp Arg
                485                 490                 495

Lys Pro Leu Tyr His Tyr Gly Arg Gly Met Asn Pro Ala Asp Lys Pro
            500                 505                 510

Ala Trp Ala Arg Glu Val Glu Glu Arg Thr Arg Met Asn Lys Gln Gln
        515                 520                 525

Asn Ser Pro Leu Ala Lys Ser Lys Pro Gly Ser Thr Gly Pro Glu Pro
    530                 535                 540

Pro Ile Pro Gln Ala Ser Pro Gly Pro Pro Gly Pro Leu Ser Gln Thr
545                 550                 555                 560

Pro Pro Met Gln Arg Pro Val Glu Pro Gln Glu Gly Pro His Lys Ser
                565                 570                 575

Leu Val Ala His Arg Val Pro Leu Lys Pro Tyr Ala Ala Pro Val Pro
            580                 585                 590

Arg Ser Gln Ser Leu Gln Asp Gln Pro Thr Arg Asn Leu Ala Ala Phe
        595                 600                 605

Pro Ala Ser His Asp Pro Asp Pro Ala Ile Pro Ala Pro Thr Ala Thr
    610                 615                 620
```

Pro Ser Ala Arg Gly Ala Val Ile Arg Gln Asn Ser Asp Pro Thr Ser
625 630 635 640

Glu Gly Pro Gly Pro Ser Pro Asn Pro Pro Ala Trp Val Arg Pro Asp
645 650 655

Asn Glu Ala Pro Pro Lys Val Pro Gln Arg Thr Ser Ser Ile Ala Thr
660 665 670

Ala Leu Asn Thr Ser Gly Ala Gly Gly Ser Arg Pro Ala Gln Ala Val
675 680 685

Arg Ala Arg Pro Arg Ser Asn Ser Ala Trp Gln Ile Tyr Leu Gln Arg
690 695 700

Arg Ala Glu Arg Gly Thr Pro Lys Pro Pro Gly Pro Pro Ala Gln Pro
705 710 715 720

Pro Gly Pro Pro Asn Ala Ser Ser Asn Pro Asp Leu Arg Arg Ser Asp
725 730 735

Pro Gly Trp Glu Arg Ser Asp Ser Val Leu Pro Ala Ser His Gly His
740 745 750

Leu Pro Gln Ala Gly Ser Leu Glu Arg Asn Arg Val Gly Val Ser Ser
755 760 765

Lys Pro Asp Ser Ser Pro Val Leu Ser Pro Gly Asn Lys Ala Lys Pro
770 775 780

Asp Asp His Arg Ser Arg Pro Gly Arg Pro Ala Asp Phe Val Leu Leu
785 790 795 800

Lys Glu Arg Thr Leu Asp Glu Ala Pro Arg Pro Pro Lys Lys Ala Met
805 810 815

Asp Tyr Ser Ser Ser Ser Glu Glu Val Glu Ser Ser Glu Asp Asp Glu
820 825 830

Glu Glu Gly Glu Gly Gly Pro Ala Glu Gly Ser Arg Asp Thr Pro Gly
835 840 845

Gly Arg Asp Gly Asp Thr Asp Ser Val Ser Thr Met Val Val His Asp
850 855 860

Val Glu Glu Ile Thr Gly Thr Gln Pro Pro Tyr Gly Gly Gly Thr Met
865 870 875 880

Val Val Gln Arg Thr Pro Glu Glu Glu Arg Asn Leu Leu His Ala Asp
885 890 895

Ser Asn Gly Tyr Thr Asn Leu Pro Asp Val Val Gln Pro Ser His Ser
900 905 910

Pro Thr Glu Asn Ser Lys Gly Gln Ser Pro Pro Ser Lys Asp Gly Ser

```
        915                 920                 925

Gly Asp Tyr Gln Ser Arg Gly Leu Val Lys Ala Pro Gly Lys Ser Ser
    930                 935                 940

Phe Thr Met Phe Val Asp Leu Gly Ile Tyr Gln Pro Gly Gly Ser Gly
945                 950                 955                 960

Asp Ser Ile Pro Ile Thr Ala Leu Val Gly Gly Glu Gly Thr Arg Leu
                965                 970                 975

Asp Gln Leu Gln Tyr Asp Val Arg Lys Gly Ser Val Val Asn Val Asn
            980                 985                 990

Pro Thr Asn Thr Arg Ala His Ser Glu Thr Pro Glu Ile Arg Lys Tyr
        995                 1000                1005

Lys Lys Arg Phe Asn Ser Glu Ile Leu Cys Ala Ala Leu Trp Gly Val
    1010                1015                1020

Asn Leu Leu Val Gly Thr Glu Asn Gly Leu Met Leu Leu Asp Arg Ser
1025                1030                1035                1040

Gly Gln Gly Lys Val Tyr Gly Leu Ile Gly Arg Arg Arg Phe Gln Gln
                1045                1050                1055

Met Asp Val Leu Glu Gly Leu Asn Leu Leu Ile Thr Ile Ser Gly Lys
            1060                1065                1070

Arg Asn Lys Leu Arg Val Tyr Tyr Leu Ser Trp Leu Arg Asn Lys Ile
        1075                1080                1085

Leu His Asn Asp Pro Glu Val Glu Lys Lys Gln Gly Trp Thr Thr Val
    1090                1095                1100

Gly Asp Met Glu Gly Cys Gly His Tyr Arg Val Val Lys Tyr Glu Arg
1105                1110                1115                1120

Ile Lys Phe Leu Val Ile Ala Leu Lys Ser Ser Val Glu Val Tyr Ala
                1125                1130                1135

Trp Ala Pro Lys Pro Tyr His Lys Phe Met Ala Phe Lys Ser Phe Ala
            1140                1145                1150

Asp Leu Pro His Arg Pro Leu Leu Val Asp Leu Thr Val Glu Glu Gly
        1155                1160                1165

Gln Arg Leu Lys Val Ile Tyr Gly Ser Ser Ala Gly Phe His Ala Val
    1170                1175                1180

Asp Val Asp Ser Gly Asn Ser Tyr Asp Ile Tyr Ile Pro Val His Ile
1185                1190                1195                1200

Gln Ser Gln Ile Thr Pro His Ala Ile Ile Phe Leu Pro Asn Thr Asp
```

1205 1210 1215

Gly Met Glu Met Leu Leu Cys Tyr Glu Asp Glu Gly Val Tyr Val Asn
1220 1225 1230

Thr Tyr Gly Arg Ile Ile Lys Asp Val Val Leu Gln Trp Gly Glu Met
1235 1240 1245

Pro Thr Ser Val Ala Tyr Ile Cys Ser Asn Gln Ile Met Gly Trp Gly
1250 1255 1260

Glu Lys Ala Ile Glu Ile Arg Ser Val Glu Thr Gly His Leu Asp Gly
1265 1270 1275 1280

Val Phe Met His Lys Arg Ala Gln Arg Leu Lys Phe Leu Cys Glu Arg
1285 1290 1295

Asn Asp Lys Val Phe Phe Ala Ser Val Arg Ser Gly Gly Ser Ser Gln
1300 1305 1310

Val Tyr Phe Met Thr Leu Asn Arg Asn Arg Ile Met Asn Trp
1315 1320 1325

<210> 16
<211> 349
<212> PRT
<213> Mammalian (Human) ZC4

<400> 16

Asn Val Asn Pro Leu Tyr Val Ser Pro Ala Cys Lys Lys Pro Leu Ile
1 5 10 15

His Met Tyr Glu Lys Glu Phe Thr Ser Glu Ile Cys Cys Gly Ser Leu
20 25 30

Trp Gly Val Asn Leu Leu Leu Gly Thr Arg Ser Asn Leu Tyr Leu Met
35 40 45

Asp Arg Ser Gly Lys Ala Asp Ile Thr Lys Leu Ile Arg Arg Arg Pro
50 55 60

Phe Arg Gln Ile Gln Val Leu Glu Pro Leu Asn Leu Leu Ile Thr Ile
65 70 75 80

Ser Gly His Lys Asn Arg Leu Arg Val Tyr His Leu Thr Trp Leu Arg
85 90 95

Asn Lys Ile Leu Asn Asn Asp Pro Glu Ser Lys Arg Arg Gln Glu Glu
100 105 110

Met Leu Lys Thr Glu Glu Ala Cys Lys Ala Ile Asp Lys Leu Thr Gly
115 120 125

Cys Glu His Phe Ser Val Leu Gln His Glu Glu Thr Thr Tyr Ile Ala
    130   135   140

Ile Ala Leu Lys Ser Ser Ile His Leu Tyr Ala Trp Ala Pro Lys Ser
145   150   155   160

Phe Asp Glu Ser Thr Ala Ile Lys Val Phe Pro Thr Leu Asp His Lys
                165   170   175

Pro Val Thr Val Asp Leu Ala Ile Gly Ser Glu Lys Arg Leu Lys Ile
            180   185   190

Phe Phe Ser Ser Ala Asp Gly Tyr His Leu Ile Asp Ala Glu Ser Glu
        195   200   205

Val Met Ser Asp Val Thr Leu Pro Lys Asn Pro Leu Glu Ile Ile Ile
    210   215   220

Pro Gln Asn Ile Ile Ile Leu Pro Asp Cys Leu Gly Ile Gly Met Met
225   230   235   240

Leu Thr Phe Asn Ala Glu Ala Leu Ser Val Glu Ala Asn Glu Gln Leu
                245   250   255

Phe Lys Lys Ile Leu Glu Met Trp Lys Asp Ile Pro Ser Ser Ile Ala
            260   265   270

Phe Glu Cys Thr Gln Arg Thr Thr Gly Trp Gly Gln Lys Ala Ile Glu
        275   280   285

Val Arg Ser Leu Gln Ser Arg Val Leu Glu Ser Glu Leu Lys Arg Arg
    290   295   300

Ser Ile Lys Lys Leu Arg Phe Leu Cys Thr Arg Gly Asp Lys Leu Phe
305   310   315   320

Phe Thr Ser Thr Leu Arg Asn His His Ser Arg Val Tyr Phe Met Thr
                325   330   335

Leu Gly Lys Leu Glu Glu Leu Gln Ser Asn Tyr Asp Val
            340   345

<210> 17
<211> 4023
<212> DNA
<213> Mammalian (Human) KHS2

<400> 17

ccgccatgaa ccccggcttc gatttgtccc gccggaaccc gcaggaggac ttcgagctga 60
ttcagcgcat cggcagcggc acctacggcg acgtctacaa ggcacggaat gttaacactg 120
gtgaattagc agcaattaaa gtaataaaat tggaaccagg agaagacttt gcagttgtgc 180
agcaagaaat tattatgatg aaagactgta aacacccaaa tattgttgct tattttggaa 240

gctatctcag gcgagataag ctttggattt gcatggagtt ttgtggaggt ggttctttac 300
aggatattta tcacgtaact ggacctctgt cagaactgca aattgcatat gttagcagag 360
aaacactgca gggattatat tatcttcaca gtaaaggaaa aatgcacaga gatataaagg 420
gagctaacat tctattaacg gataatggtc atgtgaaatt ggctgatttt ggagtatctg 480
cacagataac agctacaatt gccaaacgga agtctttcat tggcacacca tattggatgg 540
ctccagaagt tgcagctgtt gagaggaagg ggggttacaa tcaactctgt gatctctggg 600
cagtgggaat cactgccata gaacttgcag agcttcagcc tcctatgttt gacttacacc 660
caatgagagc attatttcta atgacaaaaa gcaattttca gcctcctaaa ctaaaggata 720
aaatgaaatg gtcaaatagt tttcatcact ttgtgaaaat ggcacttacc aaaaatccga 780
aaaaaagacc tactgctgaa aaattattac agcatccttt tgtaacacaa catttgacac 840
ggtctttggc aatcgagctg ttggataaag taaataatcc agatcattcc acttaccatg 900
atttcgatga tgatgatcct gagcctcttg ttgctgtacc acatagaatt cactcaacaa 960
gtagaaacgt gagagaagaa aaaacacgct cagagataac ctttggccaa gtgaaatttg 1020
atccacccctt aagaaaggag acagaaccac atcatgaact tcccgacagt gatggttttt 1080
tggacagttc agaagaaata tactacactg caagatctaa tctggatctg caactggaat 1140
atggacaagg acaccaaggt ggttactttt taggtgcaaa caagagtctt ctcaagtctg 1200
ttgaagaaga attgcatcag cgaggacacg tcgcacattt agaagatgat gaaggagatg 1260
atgatgaatc taaacactca actctgaaag caaaaattcc acctcctttg ccaccaaagc 1320
ctaagtctat cttcatacca caggaaatgc attctactga ggatgaaaat caaggaacaa 1380
tcaagagatg tcccatgtca gggagcccag caaagccatc ccaagttcca cctagaccac 1440
cacctcccag attacccccca cacaaacctg ttgccttagg aaatggaatg agctccttcc 1500
agttaaatgg tgaacgagat ggctcattat gtcaacaaca gaatgaacat agaggcacaa 1560
acctttcaag aaaagaaaag aaagatgtac caaagcctat tagtaatggt cttcctccaa 1620
cacctaaagt gcatatgggt gcatgttttt caaaagtttt taatgggtgt cccttgaaaa 1680
ttcactgtgc atcatcatgg ataaacccag atacaagaga tcagtacttg atatttggtg 1740
ccgaagaagg gatttatacc ctcaatctta atgaacttca tgaaacatca atggaacagc 1800
tattccctcg aaggtgtaca tggttgtatg taatgaacaa ttgcttgcta tcaatatctg 1860
gtaaagcttc tcagctttat tcccataatt taccagggct ttttgattat gcaagacaaa 1920
tgcaaaagtt acctgttgct attccagcac acaaactccc tgacagaata ctgccaagga 1980
aattttctgt atcagcaaaa atccctgaaa ccaaatggtg ccagaagtgt tgtgttgtaa 2040
gaaatcctta cacgggccat aaatacctat gtggagcact tcagactagc attgttctat 2100
tagaatgggt tgaaccaatg cagaaattta tgttaattaa gcacatagat tttcctatac 2160
catgtccact tagaatgttt gaaatgctgg tagttcctga acaggagtac cctttagttt 2220
gtgttggtgt cagtagaggt agagacttca accaagtggt tcgatttgag acggtcaatc 2280
caaattctac ctcttcatgg tttacagaat cagatacccc acagacaaat gttactcatg 2340
taacccaact ggagagagat accatccttg tatgcttgga ctgttgtata aaaatagtaa 2400
atctccaagg aagattaaaa tctagcagga aattgtcatc agaactcacc tttgatttcc 2460
agattgaatc aatagtgtgc ctacaagaca gtgtgctagc tttctggaaa catggaatgc 2520
aaggtagaag ttttagatct aatgaggtaa cacaagaaat ttcagatagc acaagaattt 2580
tcaggctgct tggatctgac agggtcgtgg ttttggaaag taggccaact gataacccca 2640
cagcaaatag caatttgtac atcctggcgg gtcatgaaaa cagttactga gaattgttgt 2700
gctttgacag ttaactctag aaagaaagaa cactaccact gcaacattaa tggatgcttg 2760
aagctgtaca aaagctgcag taacctgtct tcagttactt tgtaatttat tgtggcatga 2820
gataagatgg ggaaaatttt gttttaagtg gtatggatat atttagcata ttgaaccaca 2880
caagtgctta attcattgtt atgtaatctt tgtacatata ggcagtattt tttctgtgaa 2940
acttcatatt gctgaagaca tacactaaga atttatgtag ataatgtact tttatgagat 3000
gtacaagtaa gtgtcttatc tgtacagatg taaatgttga tgaaaatgca attggggtta 3060
atattttaag aattctttag tatattcttg ggtgtggcta tattacaaaa tgggatgctg 3120
gcaatgaaac aatacattta acactattgt atttttatta tatgtaattt agtaatatga 3180
atataaatct tgtaactttt aaaattgtaa tggaggctgt aatcatttta taatcttttt 3240
aattttaatg caagtacact ggtgtttata tttgcacaaa gtattgatat gtgatgtatt 3300
aagtcacaaa agtaagctgt gacattgtct ataagcattt ggctccacaa atgtatttgg 3360
attgttttct atgtgaagca aaccaattat aattaaccac atgttgtagt aactggtctt 3420
tttatattta agcagaatcc tgtaagattg cttgtctttg cttaaaaaca atacctttga 3480
acatttttga atcacagaat agcggtacca tgatagaata ctgcaattgt ggtcagaatt 3540
acagtatgca caaagaatta attagcatta ttaaagagtc ctcacctaaac atttcatatg 3600

```
atcacactga agaactgtaa cattccatag agtgaagtgg ttcaaatttc tcttggaatt     3660
tttacttttg ttggccttat tttatgatcc ttttcatatt tcttttgact tagagtatta     3720
atacatggcc aaaataattt agttactacc tcatacaaac aatataatgg ttactacaca     3780
tcacaggaac ttagttttgg tttaagtcat ttttgattgc ttttttccaa tggaatatgt     3840
atataccagg ttttagcaaa atgcacactt ttggctcttt ttggtatatg ttctttatat     3900
tttaatgtga gtatatacac taagaacaaa ctaaattgtg atttatgatc ttcatttatt     3960
ttaatgataa tggttttaaa atatgttcct gattgtacat attgtaaaat aaacatgttt     4020
ttt                                                                   4023
```

<210> 18
<211> 894
<212> PRT
<213> Mammalian (Human) KHS2

<400> 18

```
Met Asn Pro Gly Phe Asp Leu Ser Arg Arg Asn Pro Gln Glu Asp Phe
1               5                   10                  15

Glu Leu Ile Gln Arg Ile Gly Ser Gly Thr Tyr Gly Asp Val Tyr Lys
            20                  25                  30

Ala Arg Asn Val Asn Thr Gly Glu Leu Ala Ala Ile Lys Val Ile Lys
        35                  40                  45

Leu Glu Pro Gly Glu Asp Phe Ala Val Val Gln Gln Glu Ile Ile Met
    50                  55                  60

Met Lys Asp Cys Lys His Pro Asn Ile Val Ala Tyr Phe Gly Ser Tyr
65                  70                  75                  80

Leu Arg Arg Asp Lys Leu Trp Ile Cys Met Glu Phe Cys Gly Gly Gly
                85                  90                  95

Ser Leu Gln Asp Ile Tyr His Val Thr Gly Pro Leu Ser Glu Leu Gln
            100                 105                 110

Ile Ala Tyr Val Ser Arg Glu Thr Leu Gln Gly Leu Tyr Tyr Leu His
        115                 120                 125

Ser Lys Gly Lys Met His Arg Asp Ile Lys Gly Ala Asn Ile Leu Leu
    130                 135                 140

Thr Asp Asn Gly His Val Lys Leu Ala Asp Phe Gly Val Ser Ala Gln
145                 150                 155                 160

Ile Thr Ala Thr Ile Ala Lys Arg Lys Ser Phe Ile Gly Thr Pro Tyr
                165                 170                 175

Trp Met Ala Pro Glu Val Ala Ala Val Glu Arg Lys Gly Gly Tyr Asn
            180                 185                 190

Gln Leu Cys Asp Leu Trp Ala Val Gly Ile Thr Ala Ile Glu Leu Ala
        195                 200                 205
```

Glu Leu Gln Pro Pro Met Phe Asp Leu His Pro Met Arg Ala Leu Phe
210 215 220

Leu Met Thr Lys Ser Asn Phe Gln Pro Pro Lys Leu Lys Asp Lys Met
225 230 235 240

Lys Trp Ser Asn Ser Phe His His Phe Val Lys Met Ala Leu Thr Lys
245 250 255

Asn Pro Lys Lys Arg Pro Thr Ala Glu Lys Leu Leu Gln His Pro Phe
260 265 270

Val Thr Gln His Leu Thr Arg Ser Leu Ala Ile Glu Leu Leu Asp Lys
275 280 285

Val Asn Asn Pro Asp His Ser Thr Tyr His Asp Phe Asp Asp Asp Asp
290 295 300

Pro Glu Pro Leu Val Ala Val Pro His Arg Ile His Ser Thr Ser Arg
305 310 315 320

Asn Val Arg Glu Glu Lys Thr Arg Ser Glu Ile Thr Phe Gly Gln Val
325 330 335

Lys Phe Asp Pro Pro Leu Arg Lys Glu Thr Glu Pro His His Glu Leu
340 345 350

Pro Asp Ser Asp Gly Phe Leu Asp Ser Ser Glu Glu Ile Tyr Tyr Thr
355 360 365

Ala Arg Ser Asn Leu Asp Leu Gln Leu Glu Tyr Gly Gln Gly His Gln
370 375 380

Gly Gly Tyr Phe Leu Gly Ala Asn Lys Ser Leu Leu Lys Ser Val Glu
385 390 395 400

Glu Glu Leu His Gln Arg Gly His Val Ala His Leu Glu Asp Asp Glu
405 410 415

Gly Asp Asp Asp Glu Ser Lys His Ser Thr Leu Lys Ala Lys Ile Pro
420 425 430

Pro Pro Leu Pro Pro Lys Pro Lys Ser Ile Phe Ile Pro Gln Glu Met
435 440 445

His Ser Thr Glu Asp Glu Asn Gln Gly Thr Ile Lys Arg Cys Pro Met
450 455 460

Ser Gly Ser Pro Ala Lys Pro Ser Gln Val Pro Pro Arg Pro Pro Pro
465 470 475 480

Pro Arg Leu Pro Pro His Lys Pro Val Ala Leu Gly Asn Gly Met Ser
485 490 495

Ser Phe Gln Leu Asn Gly Glu Arg Asp Gly Ser Leu Cys Gln Gln Gln

500 505 510

Asn Glu His Arg Gly Thr Asn Leu Ser Arg Lys Glu Lys Lys Asp Val
515 520 525

Pro Lys Pro Ile Ser Asn Gly Leu Pro Pro Thr Pro Lys Val His Met
530 535 540

Gly Ala Cys Phe Ser Lys Val Phe Asn Gly Cys Pro Leu Lys Ile His
545 550 555 560

Cys Ala Ser Ser Trp Ile Asn Pro Asp Thr Arg Asp Gln Tyr Leu Ile
565 570 575

Phe Gly Ala Glu Glu Gly Ile Tyr Thr Leu Asn Leu Asn Glu Leu His
580 585 590

Glu Thr Ser Met Glu Gln Leu Phe Pro Arg Arg Cys Thr Trp Leu Tyr
595 600 605

Val Met Asn Asn Cys Leu Leu Ser Ile Ser Gly Lys Ala Ser Gln Leu
610 615 620

Tyr Ser His Asn Leu Pro Gly Leu Phe Asp Tyr Ala Arg Gln Met Gln
625 630 635 640

Lys Leu Pro Val Ala Ile Pro Ala His Lys Leu Pro Asp Arg Ile Leu
645 650 655

Pro Arg Lys Phe Ser Val Ser Ala Lys Ile Pro Glu Thr Lys Trp Cys
660 665 670

Gln Lys Cys Cys Val Val Arg Asn Pro Tyr Thr Gly His Lys Tyr Leu
675 680 685

Cys Gly Ala Leu Gln Thr Ser Ile Val Leu Leu Glu Trp Val Glu Pro
690 695 700

Met Gln Lys Phe Met Leu Ile Lys His Ile Asp Phe Pro Ile Pro Cys
705 710 715 720

Pro Leu Arg Met Phe Glu Met Leu Val Val Pro Glu Gln Glu Tyr Pro
725 730 735

Leu Val Cys Val Gly Val Ser Arg Gly Arg Asp Phe Asn Gln Val Val
740 745 750

Arg Phe Glu Thr Val Asn Pro Asn Ser Thr Ser Ser Trp Phe Thr Glu
755 760 765

Ser Asp Thr Pro Gln Thr Asn Val Thr His Val Thr Gln Leu Glu Arg
770 775 780

Asp Thr Ile Leu Val Cys Leu Asp Cys Cys Ile Lys Ile Val Asn Leu
785 790 795 800

Gln Gly Arg Leu Lys Ser Ser Arg Lys Leu Ser Ser Glu Leu Thr Phe
805 810 815

Asp Phe Gln Ile Glu Ser Ile Val Cys Leu Gln Asp Ser Val Leu Ala
820 825 830

Phe Trp Lys His Gly Met Gln Gly Arg Ser Phe Arg Ser Asn Glu Val
835 840 845

Thr Gln Glu Ile Ser Asp Ser Thr Arg Ile Phe Arg Leu Leu Gly Ser
850 855 860

Asp Arg Val Val Val Leu Glu Ser Arg Pro Thr Asp Asn Pro Thr Ala
865 870 875 880

Asn Ser Asn Leu Tyr Ile Leu Ala Gly His Glu Asn Ser Tyr
885 890

<210> 19
<211> 4196
<212> DNA
<213> Mammalian (Human) SULU1

<400> 19

gggagggtcc ttgtggcgcc gggcggcggg gtcctgcgtg gagagtggga cgcaacgccg 60
agaccgcgag cagaggctgc gcacagccgg atccggcact cagcgaccgg acccaaggat 120
ccgccgggga acaagccaca ggagagcgac tcaggaacaa gtgtgggaga ggaagcggcg 180
gcggcggcgc cgggcccggg ggtggtgaca gcaggtctga ggttgcatca taaatacaaa 240
ggactgaagt tataaaagag aaaagagaag tttgctgcta aaatgaatct gagcaatatg 300
gaatattttg tgccacacac aaaaaggtac tgaagattta ccccccaaaa aaaattgtca 360
atgagaaata aagctaactg atatcaaaaa gcagagcctg ctctactggc catcatgcgt 420
aaaggggtgc tgaaggaccc agagattgac gatctattct acaaagatga tcctgaggaa 480
ctttttattg gtttgcatga aattggacat ggaagttttg gagcagttta ttttgctaca 540
aatgctcaca ccaatgaggt ggtggcaatt aagaagatgt cctatagtgg gaagcagacc 600
catgagaaat ggcaagatat tcttaaggaa gttaaatttt tacgacaatt gaagcatcct 660
aatactattg agtacaaagg ctgttacttg aaagaacaca ctgcttggtt ggtgatggaa 720
tattgcttag gctcagcctc tgatttatta gaagttcata aaaaaccact tcaggaagtg 780
gagatcgctg ccattactca tggagccttg catggactag cctacctaca ttctcatgca 840
ttgattcata gggatattaa agcaggaaat attcttctaa cagagccagg tcaggtaaaa 900
ctagctgatt ttggatctgc ttcaatggct tctcctgcca actccttcgt gggcacacct 960
tactggatgg ctccagaggt gatcttagct atggatgaag gacagtatga tgggaaagtt 1020
gatatttggt cacttggcat cacttgtatt gaattggcgg aacggaagcc gccccttttc 1080
aacatgaatg caatgagtgc cttatatcac attgcccaga atgactcccc aacgttacag 1140
tctaatgaat ggacagactc ctttaggaga tttgttgatt actgcttgca gaaaatacct 1200
caggaaaggc caacatcagc agaactatta aggcatgact ttgttcgacg agaccggcca 1260
ctacgtgtcc tcattgacct catacagagg acaaaagatg cagttcgtga gctagataac 1320
ctacagtacc gaaaaatgaa aaaaatactt ttccaagaga cacggaatgg acccttgaat 1380
gagtcacagg aggatgagga agacagtgaa catggaacca gcctgaacag ggaaatggac 1440
agcctgggca gcaaccattc cattccaagc atgtccgtga gcacaggcag ccagagcagc 1500
agtgtgaaca gcatgcagga agtcatggac gagagcagtt ccgaacttgt catgatgcac 1560
gatgacgaaa gcacaatcaa ttccagctcc tccgtcgtgc ataagaaaga tcatgtattc 1620

```
acaagggatg aggcgggcca cggcgatccc aggcctgagc cgcggcctac ccagtcagtt    1680
cagagccagg ccctccacta ccggaacaga gagcgctttg ccacgatcaa atcagcatct    1740
ttggttacac gacagatcca tgagcatgag caggagaacg agttgcggga acagatgtca    1800
ggttataagc ggatgcggcg ccagcaccag aagcagctga tcgccctgga gaacaagctg    1860
aaggctgaga tggacgagca ccgcctcaag ctacagaagg aggtggagac gcatgccaac    1920
aactcgtcca tcgagctgga gaagctggcc aagaagcaag tggctatcat agaaaaggag    1980
gcaaaggtag ctgcagcaga tgagaagaag ttccagcaac agatcttggc ccagcagaag    2040
aaagatttga caactttctt agaaagtcag aagaagcagt ataagatttg taaggaaaaa    2100
ataaaagagg aaatgaatga ggaccatagc acacccaaga aagagaagca agagcggatc    2160
tccaaacata aagagaactt gcagcacaca caggctgaag aggaagccca ccttctcact    2220
caacagagac tgtactacga caaaaattgt cgtttcttca agcggaaaat aatgatcaag    2280
cggcacgagg tggagcagca gaacattcgg gaggaactaa ataaaaagag gacccagaag    2340
gagatggagc atgccatgct aatccggcac gacgagtcca cccgagagct agagtacagg    2400
cagctgcaca cgttacagaa gctacgcatg gatctgatcc gtttacagca ccagacggaa    2460
ctggaaaacc agctggagta caataagagg cgagaaagag aactgcacag aaagcatgtc    2520
atgggacttc ggcaacagcc aaaaaactta aaggccatgg aaatgcaaat taaaaaacag    2580
tttcaggaca cttgcaaagt acagaccaaa cagtataaag cactcaagaa tcaccagttg    2640
gaagttactc caaagaatga gcacaaaaca atcttaaaga cactgaaaga tgagcagaca    2700
agaaaacttg ccattttggc agagcagtat gaacagagta taaatgaaat gatggcctct    2760
caagcgttac ggctagatga ggctcaagaa gcagaatgcc aggccttgag gctacagctc    2820
cagcaggaaa tggagctgct caacgcctac cagagcaaaa tcaagatgca aacagaggca    2880
caacatgaac gtgagctcca gaagctagag cagagagtgt ctctgcgcag agcacacctt    2940
gagcagaaga ttgaagagga gctggctgcc cttcagaagg aacgcagcga gagaataaag    3000
aacctattgg aaaggcaaga gcgagagatt gaaacttttg acatggagag cctcagaatg    3060
ggatttggga atttggttac attagatttt cctaaggagg actacagatg agattaaatt    3120
ttttgccatt tacaaaaaaa aaaaaaaaaa agaaaacaga aaaaaattca gaccctgcaa    3180
aaccacattc cccattttaa cgggcgttgc tctcactctc tctctctctt actcttactg    3240
acatcgtgtc ggactagtgc ctgtttattc ttactccatc aggggccccc ttcctccccc    3300
cgtgtcaact ttcagtgctg gccaaaacct ggccgtctct tctattcaca gtacacgtca    3360
cagtattgat gtgattcaaa atgtttcagt gaaaactttg gagacagttt taacaaaacc    3420
aataaaccaa caacaaaaaa agtggatgta tattgcttta agcaatcact cattaccacc    3480
aatctgtgaa agtaaagcaa aaaataataa taataaatgc caagggggag agagacacaa    3540
tatccgcagc cttacacctt aactagctgc tgcattattt tattttattt tatttttttg    3600
gtatttattc atcaggaata aaaaaaacaa agttttatta aagattgaaa atttgataca    3660
ttttacagaa actaattgtg atgtacatat cagtggtgac atattattac tttttggggg    3720
acgggggtg ggtggggtga agagatcttg tgatttttaa gaacctgctg gcaagagttt     3780
aacttgtctt cagcatattc tgattgtatc ataatcattt tctgctgttg cagaggatgt    3840
gaatacactt aaggagctca cagaatccca gtagcacaaa ttgggctttg gcaaatcgtg    3900
tattttgtgt atagaaggaa tttaaggaga ggtattactt attttcatat tgtattttaa    3960
ctgtttctct gatcaaattt ttttacttcc tcctcctgtt cctccccacc tccctccttt    4020
tccagttcag tatttggagt tcaacactgt ctctcaatca gatcatcttg atctttttct    4080
ttatctccct tccccttcct aagtcccatt tcttggtcat aaatattgca ttattcacac    4140
tttcaaactg tgtattttct tacaataaaa aatgatgaaa aaaaaaaaaa aaaaaa        4196
```

<210> 20
<211> 3824
<212> DNA
<213> Mammalian (Human) SULU3

<400> 20

```
tattgaattg gcggaacgga agcctccttt atttaatatg aatgcaatga gtgccttata      60
tcacatagcc caaaatgaat cccctacact acagtctaat gaatggtctg attattttcg     120
caactttgta gattcttgcc tccagaaaat ccctcaagat cgacctacat cagaggaact     180
```

tttaaagcac atatttgttc ttcgggagcg ccctgaaacc gtgttaatag atctcattca 240
gaggacaaag gatgcagtaa gagagctgga caatctgcag tatcgaaaga tgaagaaact 300
ccttttccag gaggcacata atggaccagc agtagaagca caggaagaag aagaggaaca 360
agatcatggt gttggccgga caggaacagt taatagtgtt ggaagtaatc aatccattcc 420
cagcatgtcc atcagtgcca gcagccaaag cagtagtgtt aacagtcttc cagatgtctc 480
agatgacaag agtgagctag acatgatgga gggagaccac acagtgatgt ctaacagttc 540
tgttatccat ttaaaaccag aggaagaaaa ttacagagaa gagggagatc ctagaacaag 600
agcatcagat ccacaatctc caccccaagt atctcgtcac aaatcacact atcgtaatcg 660
agaacacttt gctactatac ggacagcatc actggttacg aggcaaatgc aagaacatga 720
gcaggactct gagcttagag aacaaatgtc tggctataag cgaatgaggc gacaacatca 780
aaagcaactg atgactctgg aaaacaagct aaaggctgag atggatgaac atcgcctcag 840
attagacaaa gatcttgaaa ctcagcgtaa caattttgct gcagaaatgg agaaacttat 900
caagaaacac caggctgcca tggagaaaga ggctaaagtg atgtccaatg aagagaaaaa 960
atttcagcaa catattcagg cccaacagaa gaaagaactg aatagttttc tcgagtccca 1020
gaaaagagag tataaacttc gaaaagagca gcttaaagag gagctaaatg aaaaccagag 1080
taccccccaaa aaagaaaaac aggagtggct ttcaaagcag aaggagaata tacagcattt 1140
ccaagcagaa gaagaagcta accttcttcg acgtcaaaga caatacctag agctggaatg 1200
ccgtcgcttc aagagaagaa tgttacttgg gcgtcataac ttagagcagg accttgtcag 1260
ggaggagtta aacaaaagac agactcagaa ggacttagag catgccatgc tactccgaca 1320
gcatgaatct atgcaagaac tggagttccg ccacctcaac acaattcaga agatgcgctg 1380
tgagttgatc agattacagc atcaaactga gctcactaac cagctggaat ataataagcg 1440
aagagaacga gaactaagac gaaagcatgt catggaagtt cgacaacagc ctaagagttt 1500
gaagtctaaa gaactccaaa taaaaaagca gtttcaggat acctgcaaaa tccaaaccag 1560
acagtacaaa gcattaagaa atcacctgct ggagactaca ccaaagagtg agcacaaagc 1620
tgttctgaaa cggctcaagg aggaacagac ccggaaatta gctatcttgg ctgagcagta 1680
tgatcacagc attaatgaaa tgctctccac acaagccctg cgtttggatg aagcacagga 1740
agcagagtgc caggttttga agatgcagct gcagcaggaa ctggagctgt tgaatgcgta 1800
tcagagcaaa atcaagatgc aagctgaggc acaacatgat cgagagcttc gcgagcttga 1860
acagagggtc tccctccgga gggcactctt agaacaaaag attgaagaag agatgttggc 1920
tttgcagaat gagcgcacag aacgaatacg aagcctgttg gaacgtcaag ccagagagat 1980
tgaagctttt gactctgaaa gcatgagact aggttttagt aatatggtcc tttctaatct 2040
ctcccctgag gcattcagcc acagctaccc gggagcttct ggttggtcac acaaccctac 2100
tggggtcca ggacctcact ggggtcatcc catgggtggc ccaccacaag cttggggcca 2160
tccaatgcaa ggtggacccc agccatgggg tcacccttca gggccaatgc aaggggtacc 2220
tcgaggtagc agtatgggag tccgcaatag cccccaggct ctgaggcgga cagcttctgg 2280
gggacggacg gagcagggca tgagcagaag cacgagtgtc acttcacaaa tatccaatgg 2340
gtcacacatg tcttatacat aacttaataa ttgagagtgg caattccgct ggagctgtct 2400
gccaaaagaa actgcctaca gacatcatca cagcagcctc ctcacttggg tactacagtg 2460
tggaagctga gtgcatatgg tatattttat tcatttttgt aaagcgttct gttttgtgtt 2520
tactaattgg gatgtcatag tacttggctg ccgggtttgt ttgtttttgg ggaaattttg 2580
aaaagtggag ttgatattaa aaataaatgt gtatgtgtgt acatatatat acacacacat 2640
acacatatat tatgcatgtg gtgaaaagaa ttggctagat aggggatttt tctgaacact 2700
gcaaaaatag aacgtagcaa aatggcttca gttatcactt ttgggtgtct gtatcctaag 2760
aagtttctga aaagatctaa agccttttta tcccatatcc caaattctta tgagccactc 2820
acagcaggca gcatatgttg aaataagtta ttactggtac acacctgcat tgcctcacca 2880
gtgtatttat ttgttattaa attgatctga cttctcagcc tcatttggac taaaaaaaga 2940
aagcagaaat ccatgaacac attgcttctc ggccttttgg ctaagatcaa gtgtagaaat 3000
ccatgaacac taaaggactt cattgatttt ttcagagagt agaaaacaac ttagtttttc 3060
tttttcctg aatgcgtcat aggcttgtga gtgattttg tccattcaat tgtgccttct 3120
ttgtattatg ataagatggg ggtacttaag gagatcacaa gttgtgtgag gattgcatta 3180
acaaacctat gagccttcaa tggggaagac cagaagggtg agaggggccc tgaaagttca 3240
tatggtgggt atgtcccgca gcagagtgag gagatgaagc ttacgtgtcc tgacgttttg 3300
ttgcttatac tgtgatatct catcctagct aagctctata atgcccaaga ccccaaacag 3360
tacttttact ttgtttgtac aaaaacaaag acatatagcc aatacaaatc aaatgccgga 3420
ggtgtttgat gccatatttg caaattgcca tctattgaaa ttctcgtcac actacataga 3480
cataattgtt atctcctttt ggcttatgtg attttctgtt tacaagtaga atagccaatt 3540

```
atttaaatgt ttagttgcca cagtgaacca ggagtcactg agccaatgac tttaccagct    3600
gctgactaat cttcatcacc actgtagatt ttgctgcatg tgcaggtcct ctatttttaa    3660
ttgctgtttt cgttgctgca gtactttaca aacttctagt tcgttgagac ttagtgacca    3720
tttggcatca agttaacatc acacaatagg aaacaccact tccacaagtc tcaagcctca    3780
gtgctaaagt actactgaaa aggaactagg aagtttggcc aatt                      3824
```

<210> 21
<211> 2249
<212> DNA
<213> Mammalian (Murine) SULU3

<400> 21

```
gcaggatgcc atcaactaac agagcaggca gtctaaagga ccctgaaatt gcagagctct      60
tcttcaaaga agatccggaa aagctcttca cagatctcag agaaatcggc catgggagct     120
ttggagcagt atattttgca cgagatgtgc gtactaatga agtggtggcc atcaagaaaa     180
tgtcttatag tggaaagcag tctactgaga aatggcagga tattattaag gaagtcaagt     240
ttctacaaag aataaaacat cccaacagta tagaatacaa aggctgctat ttacgtgaac     300
acacagcatg gcttgtaatg gaatattgtt taggatctgc ttcagattta ttagaagttc     360
ataaaaagcc attacaagaa gtggaaatag cagcaattac acatggtgct ctccagggac     420
tagcttattt acattctcat accatgatcc atagagatat caaagcagga aatatccttc     480
tgacagaacc aggccaagtg aaacttgctg actttggatc tgcttccatg gcttcccctg     540
ccaattcttt tgtgggaaca ccatattgga tggccccaga agtaatttta gccatggatg     600
aaggacagta tgatggcaaa gttgatgtat ggtctcttgg aataacgtgt attgaattag     660
ccgagaggaa gcctccttta tttaatatga atgcaatgag tgccttatat cacatagccc     720
aaaatgaatc ccctacacta caatctaata tgaatgattc ttgcctccag aaaatccctc     780
aagatcgccc tacatcagag gaacttttaa agcacatgtt tgttcttcga gagcgccctg     840
aaacagtgtt aatagatctt attcaaagga caaaggatgc agtaagagag ctggacaatc     900
tgcagtatcg aaagatgaag aaactccttt tccaggaggc acataatggg ccagcggtag     960
aagcacagga agaagaggag gagcaagatc atggtgttgg ccgaacagga acagtgaata    1020
gtgttggaag caatcagtct atccctagta tgtctatcag tgccagcagt caaagcagca    1080
gtgttaatag tcttccagat gcatcagatg acaagagtga gctagacatg atggagggag    1140
accatacagt gatgtctaac agttctgtca tccacttaaa acctgaggag gaaaattacc    1200
aggaagaagg agatcctaga acaagagcat cagacccaca gtctccccct caggtgtctc    1260
gtcacaagtc acattatcgt aatagagaac actttgcaac catacgaaca gcatcactgg    1320
ttacaagaca gatgcaagaa catgagcagg actctgaact tagagaacag atgtctggtt    1380
ataagcggat gaggcgacag catcaaaagc agctgatgac gctggaaaat aaactgaagg    1440
cagagatgga cgaacatcgg ctcagattag acaaagatct tgaaactcag cgtaacaatt    1500
tcgctgcaga aatggagaaa cttattaaga aacaccaagc tgctatggaa aaagaggcta    1560
aagtgatggc caatgaggag aaaaaattcc agcaacacat tcaggctcaa cagaaaaaag    1620
aactgaatag ctttttggag tctcaaaaaa gagaatataa acttcgcaaa gagcagctta    1680
aggaggagct gaatgaaaac cagagcacac ctaaaaaaga aaagcaggaa tggctttcaa    1740
agcagaagga gaatatacag cattttcagg cagaagaaga agctaatctt cttcgacgtc    1800
aaaggcagta tctagagcta gaatgtcgtc gcttcaaaag aagaatgtta cttgggcgac    1860
ataacttgga acaggacctt gtcagggagg agttaaacaa aaggcagact caaaaggact    1920
tggaacatgc aatgctattg cgacagcatg aatcaatgca agaactggag tttcgccatc    1980
tcaacactat tcagaagatg cgctgtgagt tgatcagact gcagcatcaa actgagctca    2040
ctaaccagct agagtacaat aagagaaggg aacgggaact gaggcgaaaa catgtcatgg    2100
aagttcgaca acaacctaag agtctgaagt ctaaagaact ccaaataaaa aagcagtttc    2160
aggatacctg caaaattcaa accagacagt acaaagcatt aaggaatcac ctactggaga    2220
ctacaccaaa gaatgagcac aaagcaatc                                       2249
```

<210> 22
<211> 898

<212> PRT
<213> Mammalian (Human) SULU1

<400> 22

Met Arg Lys Gly Val Leu Lys Asp Pro Glu Ile Asp Asp Leu Phe Tyr
1 5 10 15

Lys Asp Asp Pro Glu Glu Leu Phe Ile Gly Leu His Glu Ile Gly His
20 25 30

Gly Ser Phe Gly Ala Val Tyr Phe Ala Thr Asn Ala His Thr Asn Glu
35 40 45

Val Val Ala Ile Lys Lys Met Ser Tyr Ser Gly Lys Gln Thr His Glu
50 55 60

Lys Trp Gln Asp Ile Leu Lys Glu Val Lys Phe Leu Arg Gln Leu Lys
65 70 75 80

His Pro Asn Thr Ile Glu Tyr Lys Gly Cys Tyr Leu Lys Glu His Thr
85 90 95

Ala Trp Leu Val Met Glu Tyr Cys Leu Gly Ser Ala Ser Asp Leu Leu
100 105 110

Glu Val His Lys Lys Pro Leu Gln Glu Val Glu Ile Ala Ala Ile Thr
115 120 125

His Gly Ala Leu His Gly Leu Ala Tyr Leu His Ser His Ala Leu Ile
130 135 140

His Arg Asp Ile Lys Ala Gly Asn Ile Leu Leu Thr Glu Pro Gly Gln
145 150 155 160

Val Lys Leu Ala Asp Phe Gly Ser Ala Ser Met Ala Ser Pro Ala Asn
165 170 175

Ser Phe Val Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Ile Leu Ala
180 185 190

Met Asp Glu Gly Gln Tyr Asp Gly Lys Val Asp Ile Trp Ser Leu Gly
195 200 205

Ile Thr Cys Ile Glu Leu Ala Glu Arg Lys Pro Pro Leu Phe Asn Met
210 215 220

Asn Ala Met Ser Ala Leu Tyr His Ile Ala Gln Asn Asp Ser Pro Thr
225 230 235 240

Leu Gln Ser Asn Glu Trp Thr Asp Ser Phe Arg Arg Phe Val Asp Tyr
245 250 255

Cys Leu Gln Lys Ile Pro Gln Glu Arg Pro Thr Ser Ala Glu Leu Leu
260 265 270

Arg His Asp Phe Val Arg Arg Asp Arg Pro Leu Arg Val Leu Ile Asp
275 280 285

Leu Ile Gln Arg Thr Lys Asp Ala Val Arg Glu Leu Asp Asn Leu Gln
290 295 300

Tyr Arg Lys Met Lys Lys Ile Leu Phe Gln Glu Thr Arg Asn Gly Pro
305 310 315 320

Leu Asn Glu Ser Gln Glu Asp Glu Glu Asp Ser Glu His Gly Thr Ser
325 330 335

Leu Asn Arg Glu Met Asp Ser Leu Gly Ser Asn His Ser Ile Pro Ser
340 345 350

Met Ser Val Ser Thr Gly Ser Gln Ser Ser Ser Val Asn Ser Met Gln
355 360 365

Glu Val Met Asp Glu Ser Ser Ser Glu Leu Val Met Met His Asp Asp
370 375 380

Glu Ser Thr Ile Asn Ser Ser Ser Ser Val Val His Lys Lys Asp His
385 390 395 400

Val Phe Thr Arg Asp Glu Ala Gly His Gly Asp Pro Arg Pro Glu Pro
405 410 415

Arg Pro Thr Gln Ser Val Gln Ser Gln Ala Leu His Tyr Arg Asn Arg
420 425 430

Glu Arg Phe Ala Thr Ile Lys Ser Ala Ser Leu Val Thr Arg Gln Ile
435 440 445

His Glu His Glu Gln Glu Asn Glu Leu Arg Glu Gln Met Ser Gly Tyr
450 455 460

Lys Arg Met Arg Arg Gln His Gln Lys Gln Leu Ile Ala Leu Glu Asn
465 470 475 480

Lys Leu Lys Ala Glu Met Asp Glu His Arg Leu Lys Leu Gln Lys Glu
485 490 495

Val Glu Thr His Ala Asn Asn Ser Ser Ile Glu Leu Glu Lys Leu Ala
500 505 510

Lys Lys Gln Val Ala Ile Ile Glu Lys Glu Ala Lys Val Ala Ala Ala
515 520 525

Asp Glu Lys Lys Phe Gln Gln Gln Ile Leu Ala Gln Gln Lys Lys Asp
530 535 540

Leu Thr Thr Phe Leu Glu Ser Gln Lys Lys Gln Tyr Lys Ile Cys Lys
545 550 555 560

Glu Lys Ile Lys Glu Glu Met Asn Glu Asp His Ser Thr Pro Lys Lys

565 570 575

Glu Lys Gln Glu Arg Ile Ser Lys His Lys Glu Asn Leu Gln His Thr
580 585 590

Gln Ala Glu Glu Glu Ala His Leu Leu Thr Gln Gln Arg Leu Tyr Tyr
595 600 605

Asp Lys Asn Cys Arg Phe Phe Lys Arg Lys Ile Met Ile Lys Arg His
610 615 620

Glu Val Glu Gln Gln Asn Ile Arg Glu Glu Leu Asn Lys Lys Arg Thr
625 630 635 640

Gln Lys Glu Met Glu His Ala Met Leu Ile Arg His Asp Glu Ser Thr
645 650 655

Arg Glu Leu Glu Tyr Arg Gln Leu His Thr Leu Gln Lys Leu Arg Met
660 665 670

Asp Leu Ile Arg Leu Gln His Gln Thr Glu Leu Glu Asn Gln Leu Glu
675 680 685

Tyr Asn Lys Arg Arg Glu Arg Glu Leu His Arg Lys His Val Met Gly
690 695 700

Leu Arg Gln Gln Pro Lys Asn Leu Lys Ala Met Glu Met Gln Ile Lys
705 710 715 720

Lys Gln Phe Gln Asp Thr Cys Lys Val Gln Thr Lys Gln Tyr Lys Ala
725 730 735

Leu Lys Asn His Gln Leu Glu Val Thr Pro Lys Asn Glu His Lys Thr
740 745 750

Ile Leu Lys Thr Leu Lys Asp Glu Gln Thr Arg Lys Leu Ala Ile Leu
755 760 765

Ala Glu Gln Tyr Glu Gln Ser Ile Asn Glu Met Met Ala Ser Gln Ala
770 775 780

Leu Arg Leu Asp Glu Ala Gln Glu Ala Glu Cys Gln Ala Leu Arg Leu
785 790 795 800

Gln Leu Gln Gln Glu Met Glu Leu Leu Asn Ala Tyr Gln Ser Lys Ile
805 810 815

Lys Met Gln Thr Glu Ala Gln His Glu Arg Glu Leu Gln Lys Leu Glu
820 825 830

Gln Arg Val Ser Leu Arg Arg Ala His Leu Glu Gln Lys Ile Glu Glu
835 840 845

Glu Leu Ala Ala Leu Gln Lys Glu Arg Ser Glu Arg Ile Lys Asn Leu
850 855 860

Leu Glu Arg Gln Glu Arg Glu Ile Glu Thr Phe Asp Met Glu Ser Leu
865 870 875 880

Arg Met Gly Phe Gly Asn Leu Val Thr Leu Asp Phe Pro Lys Glu Asp
885 890 895

Tyr Arg

<210> 23
<211> 786
<212> PRT
<213> Mammalian (Human) SULU3

<400> 23

Ile Glu Leu Ala Glu Arg Lys Pro Pro Leu Phe Asn Met Asn Ala Met
1 5 10 15

Ser Ala Leu Tyr His Ile Ala Gln Asn Glu Ser Pro Thr Leu Gln Ser
20 25 30

Asn Glu Trp Ser Asp Tyr Phe Arg Asn Phe Val Asp Ser Cys Leu Gln
35 40 45

Lys Ile Pro Gln Asp Arg Pro Thr Ser Glu Glu Leu Leu Lys His Ile
50 55 60

Phe Val Leu Arg Glu Arg Pro Glu Thr Val Leu Ile Asp Leu Ile Gln
65 70 75 80

Arg Thr Lys Asp Ala Val Arg Glu Leu Asp Asn Leu Gln Tyr Arg Lys
85 90 95

Met Lys Lys Leu Leu Phe Gln Glu Ala His Asn Gly Pro Ala Val Glu
100 105 110

Ala Gln Glu Glu Glu Glu Glu Gln Asp His Gly Val Gly Arg Thr Gly
115 120 125

Thr Val Asn Ser Val Gly Ser Asn Gln Ser Ile Pro Ser Met Ser Ile
130 135 140

Ser Ala Ser Ser Gln Ser Ser Ser Val Asn Ser Leu Pro Asp Val Ser
145 150 155 160

Asp Asp Lys Ser Glu Leu Asp Met Met Glu Gly Asp His Thr Val Met
165 170 175

Ser Asn Ser Ser Val Ile His Leu Lys Pro Glu Glu Glu Asn Tyr Arg
180 185 190

Glu Glu Gly Asp Pro Arg Thr Arg Ala Ser Asp Pro Gln Ser Pro Pro
195 200 205

Gln Val Ser Arg His Lys Ser His Tyr Arg Asn Arg Glu His Phe Ala
210 215 220

Thr Ile Arg Thr Ala Ser Leu Val Thr Arg Gln Met Gln Glu His Glu
225 230 235 240

Gln Asp Ser Glu Leu Arg Glu Gln Met Ser Gly Tyr Lys Arg Met Arg
245 250 255

Arg Gln His Gln Lys Gln Leu Met Thr Leu Glu Asn Lys Leu Lys Ala
260 265 270

Glu Met Asp Glu His Arg Leu Arg Leu Asp Lys Asp Leu Glu Thr Gln
275 280 285

Arg Asn Asn Phe Ala Ala Glu Met Glu Lys Leu Ile Lys Lys His Gln
290 295 300

Ala Ala Met Glu Lys Glu Ala Lys Val Met Ser Asn Glu Glu Lys Lys
305 310 315 320

Phe Gln Gln His Ile Gln Ala Gln Gln Lys Lys Glu Leu Asn Ser Phe
325 330 335

Leu Glu Ser Gln Lys Arg Glu Tyr Lys Leu Arg Lys Glu Gln Leu Lys
340 345 350

Glu Glu Leu Asn Glu Asn Gln Ser Thr Pro Lys Lys Glu Lys Gln Glu
355 360 365

Trp Leu Ser Lys Gln Lys Glu Asn Ile Gln His Phe Gln Ala Glu Glu
370 375 380

Glu Ala Asn Leu Leu Arg Arg Gln Arg Gln Tyr Leu Glu Leu Glu Cys
385 390 395 400

Arg Arg Phe Lys Arg Arg Met Leu Leu Gly Arg His Asn Leu Glu Gln
405 410 415

Asp Leu Val Arg Glu Glu Leu Asn Lys Arg Gln Thr Gln Lys Asp Leu
420 425 430

Glu His Ala Met Leu Leu Arg Gln His Glu Ser Met Gln Glu Leu Glu
435 440 445

Phe Arg His Leu Asn Thr Ile Gln Lys Met Arg Cys Glu Leu Ile Arg
450 455 460

Leu Gln His Gln Thr Glu Leu Thr Asn Gln Leu Glu Tyr Asn Lys Arg
465 470 475 480

Arg Glu Arg Glu Leu Arg Arg Lys His Val Met Glu Val Arg Gln Gln

```
                485                 490                 495

Pro Lys Ser Leu Lys Ser Lys Glu Leu Gln Ile Lys Lys Gln Phe Gln
            500                 505                 510

Asp Thr Cys Lys Ile Gln Thr Arg Gln Tyr Lys Ala Leu Arg Asn His
        515                 520                 525

Leu Leu Glu Thr Thr Pro Lys Ser Glu His Lys Ala Val Leu Lys Arg
    530                 535                 540

Leu Lys Glu Glu Gln Thr Arg Lys Leu Ala Ile Leu Ala Glu Gln Tyr
545                 550                 555                 560

Asp His Ser Ile Asn Glu Met Leu Ser Thr Gln Ala Leu Arg Leu Asp
                565                 570                 575

Glu Ala Gln Glu Ala Glu Cys Gln Val Leu Lys Met Gln Leu Gln Gln
            580                 585                 590

Glu Leu Glu Leu Leu Asn Ala Tyr Gln Ser Lys Ile Lys Met Gln Ala
        595                 600                 605

Glu Ala Gln His Asp Arg Glu Leu Arg Glu Leu Glu Gln Arg Val Ser
    610                 615                 620

Leu Arg Arg Ala Leu Leu Glu Gln Lys Ile Glu Glu Glu Met Leu Ala
625                 630                 635                 640

Leu Gln Asn Glu Arg Thr Glu Arg Ile Arg Ser Leu Leu Glu Arg Gln
                645                 650                 655

Ala Arg Glu Ile Glu Ala Phe Asp Ser Glu Ser Met Arg Leu Gly Phe
            660                 665                 670

Ser Asn Met Val Leu Ser Asn Leu Ser Pro Glu Ala Phe Ser His Ser
        675                 680                 685

Tyr Pro Gly Ala Ser Gly Trp Ser His Asn Pro Thr Gly Gly Pro Gly
    690                 695                 700

Pro His Trp Gly His Pro Met Gly Gly Pro Pro Gln Ala Trp Gly His
705                 710                 715                 720

Pro Met Gln Gly Gly Pro Gln Pro Trp Gly His Pro Ser Gly Pro Met
                725                 730                 735

Gln Gly Val Pro Arg Gly Ser Ser Met Gly Val Arg Asn Ser Pro Gln
            740                 745                 750

Ala Leu Arg Arg Thr Ala Ser Gly Gly Arg Thr Glu Gln Gly Met Ser
        755                 760                 765

Arg Ser Thr Ser Val Thr Ser Gln Ile Ser Asn Gly Ser His Met Ser
    770                 775                 780
```

Tyr Thr
785

<210> 24
<211> 748
<212> PRT
<213> Mammalian (Murine) SULU3

<400> 24

Met Pro Ser Thr Asn Arg Ala Gly Ser Leu Lys Asp Pro Glu Ile Ala
1 5 10 15

Glu Leu Phe Phe Lys Glu Asp Pro Glu Lys Leu Phe Thr Asp Leu Arg
20 25 30

Glu Ile Gly His Gly Ser Phe Gly Ala Val Tyr Phe Ala Arg Asp Val
35 40 45

Arg Thr Asn Glu Val Val Ala Ile Lys Lys Met Ser Tyr Ser Gly Lys
50 55 60

Gln Ser Thr Glu Lys Trp Gln Asp Ile Ile Lys Glu Val Lys Phe Leu
65 70 75 80

Gln Arg Ile Lys His Pro Asn Ser Ile Glu Tyr Lys Gly Cys Tyr Leu
85 90 95

Arg Glu His Thr Ala Trp Leu Val Met Glu Tyr Cys Leu Gly Ser Ala
100 105 110

Ser Asp Leu Leu Glu Val His Lys Lys Pro Leu Gln Glu Val Glu Ile
115 120 125

Ala Ala Ile Thr His Gly Ala Leu Gln Gly Leu Ala Tyr Leu His Ser
130 135 140

His Thr Met Ile His Arg Asp Ile Lys Ala Gly Asn Ile Leu Leu Thr
145 150 155 160

Glu Pro Gly Gln Val Lys Leu Ala Asp Phe Gly Ser Ala Ser Met Ala
165 170 175

Ser Pro Ala Asn Ser Phe Val Gly Thr Pro Tyr Trp Met Ala Pro Glu
180 185 190

Val Ile Leu Ala Met Asp Glu Gly Gln Tyr Asp Gly Lys Val Asp Val
195 200 205

Trp Ser Leu Gly Ile Thr Cys Ile Glu Leu Ala Glu Arg Lys Pro Pro
210 215 220

Leu Phe Asn Met Asn Ala Met Ser Ala Leu Tyr His Ile Ala Gln Asn
225 230 235 240

Glu Ser Pro Thr Leu Gln Ser Asn Met Asn Asp Ser Cys Leu Gln Lys
245 250 255

Ile Pro Gln Asp Arg Pro Thr Ser Glu Glu Leu Leu Lys His Met Phe
260 265 270

Val Leu Arg Glu Arg Pro Glu Thr Val Leu Ile Asp Leu Ile Gln Arg
275 280 285

Thr Lys Asp Ala Val Arg Glu Leu Asp Asn Leu Gln Tyr Arg Lys Met
290 295 300

Lys Lys Leu Leu Phe Gln Glu Ala His Asn Gly Pro Ala Val Glu Ala
305 310 315 320

Gln Glu Glu Glu Glu Glu Gln Asp His Gly Val Gly Arg Thr Gly Thr
325 330 335

Val Asn Ser Val Gly Ser Asn Gln Ser Ile Pro Ser Met Ser Ile Ser
340 345 350

Ala Ser Ser Gln Ser Ser Ser Val Asn Ser Leu Pro Asp Ala Ser Asp
355 360 365

Asp Lys Ser Glu Leu Asp Met Met Glu Gly Asp His Thr Val Met Ser
370 375 380

Asn Ser Ser Val Ile His Leu Lys Pro Glu Glu Glu Asn Tyr Gln Glu
385 390 395 400

Glu Gly Asp Pro Arg Thr Arg Ala Ser Asp Pro Gln Ser Pro Pro Gln
405 410 415

Val Ser Arg His Lys Ser His Tyr Arg Asn Arg Glu His Phe Ala Thr
420 425 430

Ile Arg Thr Ala Ser Leu Val Thr Arg Gln Met Gln Glu His Glu Gln
435 440 445

Asp Ser Glu Leu Arg Glu Gln Met Ser Gly Tyr Lys Arg Met Arg Arg
450 455 460

Gln His Gln Lys Gln Leu Met Thr Leu Glu Asn Lys Leu Lys Ala Glu
465 470 475 480

Met Asp Glu His Arg Leu Arg Leu Asp Lys Asp Leu Glu Thr Gln Arg
485 490 495

Asn Asn Phe Ala Ala Glu Met Glu Lys Leu Ile Lys Lys His Gln Ala
500 505 510

Ala Met Glu Lys Glu Ala Lys Val Met Ala Asn Glu Glu Lys Lys Phe

515 520 525

Gln Gln His Ile Gln Ala Gln Gln Lys Lys Glu Leu Asn Ser Phe Leu
530 535 540

Glu Ser Gln Lys Arg Glu Tyr Lys Leu Arg Lys Glu Gln Leu Lys Glu
545 550 555 560

Glu Leu Asn Glu Asn Gln Ser Thr Pro Lys Lys Glu Lys Gln Glu Trp
565 570 575

Leu Ser Lys Gln Lys Glu Asn Ile Gln His Phe Gln Ala Glu Glu Glu
580 585 590

Ala Asn Leu Leu Arg Arg Gln Arg Gln Tyr Leu Glu Leu Glu Cys Arg
595 600 605

Arg Phe Lys Arg Arg Met Leu Leu Gly Arg His Asn Leu Glu Gln Asp
610 615 620

Leu Val Arg Glu Glu Leu Asn Lys Arg Gln Thr Gln Lys Asp Leu Glu
625 630 635 640

His Ala Met Leu Leu Arg Gln His Glu Ser Met Gln Glu Leu Glu Phe
645 650 655

Arg His Leu Asn Thr Ile Gln Lys Met Arg Cys Glu Leu Ile Arg Leu
660 665 670

Gln His Gln Thr Glu Leu Thr Asn Gln Leu Glu Tyr Asn Lys Arg Arg
675 680 685

Glu Arg Glu Leu Arg Arg Lys His Val Met Glu Val Arg Gln Gln Pro
690 695 700

Lys Ser Leu Lys Ser Lys Glu Leu Gln Ile Lys Lys Gln Phe Gln Asp
705 710 715 720

Thr Cys Lys Ile Gln Thr Arg Gln Tyr Lys Ala Leu Arg Asn His Leu
725 730 735

Leu Glu Thr Thr Pro Lys Asn Glu His Lys Ala Ile
740 745

<210> 25
<211> 2795
<212> DNA
<213> Mammalian (Human) GEK2

<400> 25

cgaagccaca gcccgagccc gagcccgagc ccgagccggc gccaccgcgc ccccggccat 60
ggcttttgcc aatttccgcc gcatcctgcg cctgtctacc ttcgagaaga gaaagtcccg 120

cgaatatgag cacgtccgcc gcgacctgga ccccaacgag gtgtgggaga tcgtgggcga 180
gctgggcgac ggcgccttcg gcaaggttta caaggccaag aataaggaga cgggtgcttt 240
ggctgcggcc aaagtcattg aaaccaagag tgaggaggag ctggaggact acatcgtgga 300
gattgagatc ctggccacct gcgaccaccc ctacattgtg aagctcctgg gagcctacta 360
tcacgacggg aagctgtgga tcatgattga gttctgtcca gggggagccg tggacgccat 420
catgctggag ctggacagag gcctcacgga gccccagata caggtggttt gccgccagat 480
gctagaagcc ctcaacttcc tgcacagcaa gaggatcatc caccgagatc tgaaagctgg 540
caacgtgctg atgaccctcg agggagacat caggctggct gactttggtg tgtctgccaa 600
gaatctgaag actctacaga aacgagattc cttcatcggc acgccttact ggatggcccc 660
cgaggtggtc atgtgtgaga ccatgaaaga cacgccctac gactacaaag ccgacatctg 720
gtccctgggc atcacgctga ttgagatggc ccagatcgag ccgccacacc acgagctcaa 780
ccccatgcgg gtcctgctaa agatcgccaa gtcggaccct cccacgctgc tcacgccctc 840
caagtggtct gtagagttcc gtgacttcct gaagatagcc ctggataaga acccagaaac 900
ccgacccagt gccgcgcagc tgctggagca tcccttcgtc agcagcatca ccagtaacaa 960
ggctctgcgg gagctggtgg ctgaggccaa ggccgaggtg atggaagaga tcgaagacgg 1020
ccgggatgag gggaagaggg aggacgccgt ggatgccgcc tccaccctgg agaaccatac 1080
tcagaactcc tctgaggtga gtccgccaag cctcaatgct gacaagcctc tcgaggagtc 1140
accttccacc ccgctggcac ccagccagtc tcaggacagt gtgaatgagc cctgcagcca 1200
gccctctggg gacagatccc tccaaaccac cagtccccca gtcgtggccc ctggaaatga 1260
gaacggcctg gcagtgcctg tgcccctgcg gaagtcccga cccgtgtcaa tggatgccag 1320
aattcaggta gcccaggaga agcaagttgc tgagcagggt ggggacctca gcccagcagc 1380
caacagatct caaaaggcca gccagagccg gcccaacagc agcgccctgg agaccttggg 1440
tggggagaag ctggccaatg gcagcctgga gccacctgcc caggcagctc cagggccttc 1500
caagagggac tcggactgca gcagcctctg cacctctgag agcatggact atggtaccaa 1560
tctctccact gacctgtcgc tgaacaaaga gatgggctct ctgtccatca aggacccgaa 1620
actgtacaaa aaaaccctca agcggacacg caaatttgtg gtggatggtg tggaggtgag 1680
catcaccacc tccaagatca tcagcgaaga tgagaagaag gatgaggaga tgagatttct 1740
caggcgccag gaactccgag agcttcggct gctccagaaa gaagagcatc ggaaccagac 1800
ccagctgagt aacaagcatg agctgcagct ggagcaaatg cataaacgtt ttgaacagga 1860
aatcaacgcc aagaagaagt tctttgacac ggaattagag aacctggagc gtcagcaaaa 1920
gcagcaagtg gagaagatgg agcaagacca tgccgtgcgc cgccgggagg aggccaggcg 1980
gatccgcctg gagcaggatc gggactacac caggttccaa gagcagctca aactgatgaa 2040
gaaagaggtg aagaacgagg tggagaagct cccccgacag cagcggaagg aaagcatgaa 2100
gcagaagatg gaggagcaca cgcagaaaaa gcagcttctt gaccgggact ttgtagccaa 2160
gcagaaggag gacctggagc tggccatgaa gaggctcacc accgacaaca ggcgggagat 2220
ctgtgacaag gagcgcgagt gcctcatgaa gaagcaggag ctccttcgag accgggaagc 2280
agccctgtgg gagatggaag agcaccagct gcaggagagg caccagctgg tgaagcagca 2340
gctcaaagac cagtacttcc tccagcggca cgagctgctg cgcaagcatg agaaggagcg 2400
ggagcagatg cagcgctaca accagcgcat gatagagcag ctgaaggtgc ggcagcaaca 2460
ggaaaaggcg cggctgccca agatccagag gagtgagggc aagacgcgca tggccatgta 2520
caagaagagc ctccacatca acggcggggg cagcgcagct gagcagcgtg agaagatcaa 2580
gcagttctcc cagcaggagg agaagaggca gaagtcggag cggctgcagc aacagcagaa 2640
acacgagaac cagatgcggg acatgctggc gcagtgcgag agcaacatga gcgagctgca 2700
gcagctgcag aatgaaaagt gccacctcct ggtagagcac gaaacccaga aactgaaggc 2760
cctggatgag agccataacc agaacctgaa ggaat 2795

<210> 26
<211> 912
<212> PRT
<213> Mammalian (Human) GEK2

<400> 26

Met Ala Phe Ala Asn Phe Arg Arg Ile Leu Arg Leu Ser Thr Phe Glu

50

1 5 10 15

Lys Arg Lys Ser Arg Glu Tyr Glu His Val Arg Arg Asp Leu Asp Pro
20 25 30

Asn Glu Val Trp Glu Ile Val Gly Glu Leu Gly Asp Gly Ala Phe Gly
35 40 45

Lys Val Tyr Lys Ala Lys Asn Lys Glu Thr Gly Ala Leu Ala Ala Ala
50 55 60

Lys Val Ile Glu Thr Lys Ser Glu Glu Glu Leu Glu Asp Tyr Ile Val
65 70 75 80

Glu Ile Glu Ile Leu Ala Thr Cys Asp His Pro Tyr Ile Val Lys Leu
85 90 95

Leu Gly Ala Tyr Tyr His Asp Gly Lys Leu Trp Ile Met Ile Glu Phe
100 105 110

Cys Pro Gly Gly Ala Val Asp Ala Ile Met Leu Glu Leu Asp Arg Gly
115 120 125

Leu Thr Glu Pro Gln Ile Gln Val Val Cys Arg Gln Met Leu Glu Ala
130 135 140

Leu Asn Phe Leu His Ser Lys Arg Ile Ile His Arg Asp Leu Lys Ala
145 150 155 160

Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg Leu Ala Asp Phe
165 170 175

Gly Val Ser Ala Lys Asn Leu Lys Thr Leu Gln Lys Arg Asp Ser Phe
180 185 190

Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Met Cys Glu Thr
195 200 205

Met Lys Asp Thr Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly
210 215 220

Ile Thr Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu
225 230 235 240

Asn Pro Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr
245 250 255

Leu Leu Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys
260 265 270

Ile Ala Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu
275 280 285

Leu Glu His Pro Phe Val Ser Ser Ile Thr Ser Asn Lys Ala Leu Arg
290 295 300

Glu Leu Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp
305 310 315 320

Gly Arg Asp Glu Gly Glu Glu Glu Asp Ala Val Asp Ala Ala Ser Thr
325 330 335

Leu Glu Asn His Thr Gln Asn Ser Ser Glu Val Ser Pro Pro Ser Leu
340 345 350

Asn Ala Asp Lys Pro Leu Glu Glu Ser Pro Ser Thr Pro Leu Ala Pro
355 360 365

Ser Gln Ser Gln Asp Ser Val Asn Glu Pro Cys Ser Gln Pro Ser Gly
370 375 380

Asp Arg Ser Leu Gln Thr Thr Ser Pro Pro Val Val Ala Pro Gly Asn
385 390 395 400

Glu Asn Gly Leu Ala Val Pro Val Pro Leu Arg Lys Ser Arg Pro Val
405 410 415

Ser Met Asp Ala Arg Ile Gln Val Ala Gln Glu Lys Gln Val Ala Glu
420 425 430

Gln Gly Gly Asp Leu Ser Pro Ala Ala Asn Arg Ser Gln Lys Ala Ser
435 440 445

Gln Ser Arg Pro Asn Ser Ser Ala Leu Glu Thr Leu Gly Gly Glu Lys
450 455 460

Leu Ala Asn Gly Ser Leu Glu Pro Pro Ala Gln Ala Ala Pro Gly Pro
465 470 475 480

Ser Lys Arg Asp Ser Asp Cys Ser Ser Leu Cys Thr Ser Glu Ser Met
485 490 495

Asp Tyr Gly Thr Asn Leu Ser Thr Asp Leu Ser Leu Asn Lys Glu Met
500 505 510

Gly Ser Leu Ser Ile Lys Asp Pro Lys Leu Tyr Lys Lys Thr Leu Lys
515 520 525

Arg Thr Arg Lys Phe Val Val Asp Gly Val Glu Val Ser Ile Thr Thr
530 535 540

Ser Lys Ile Ile Ser Glu Asp Glu Lys Lys Asp Glu Glu Met Arg Phe
545 550 555 560

Leu Arg Arg Gln Glu Leu Arg Glu Leu Arg Leu Leu Gln Lys Glu Glu
565 570 575

His Arg Asn Gln Thr Gln Leu Ser Asn Lys His Glu Leu Gln Leu Glu
580 585 590

Gln Met His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe
595 600 605

Phe Asp Thr Glu Leu Glu Asn Leu Glu Arg Gln Gln Lys Gln Gln Val
610 615 620

Glu Lys Met Glu Gln Asp His Ala Val Arg Arg Arg Glu Glu Ala Arg
625 630 635 640

Arg Ile Arg Leu Glu Gln Asp Arg Asp Tyr Thr Arg Phe Gln Glu Gln
645 650 655

Leu Lys Leu Met Lys Lys Glu Val Lys Asn Glu Val Glu Lys Leu Pro
660 665 670

Arg Gln Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Thr
675 680 685

Gln Lys Lys Gln Leu Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu
690 695 700

Asp Leu Glu Leu Ala Met Lys Arg Leu Thr Thr Asp Asn Arg Arg Glu
705 710 715 720

Ile Cys Asp Lys Glu Arg Glu Cys Leu Met Lys Lys Gln Glu Leu Leu
725 730 735

Arg Asp Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln
740 745 750

Glu Arg His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu
755 760 765

Gln Arg His Glu Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met
770 775 780

Gln Arg Tyr Asn Gln Arg Met Ile Glu Gln Leu Lys Val Arg Gln Gln
785 790 795 800

Gln Glu Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Glu Gly Lys Thr
805 810 815

Arg Met Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Gly Gly Ser
820 825 830

Ala Ala Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu
835 840 845

Lys Arg Gln Lys Ser Glu Arg Leu Gln Gln Gln Gln Lys His Glu Asn
850 855 860

Gln Met Arg Asp Met Leu Ala Gln Cys Glu Ser Asn Met Ser Glu Leu
865 870 875 880

Gln Gln Leu Gln Asn Glu Lys Cys His Leu Leu Val Glu His Glu Thr
885 890 895

```
Gln Lys Leu Lys Ala Leu Asp Glu Ser His Asn Gln Asn Leu Lys Glu
            900                 905                 910
```

<210> 27
<211> 3604
<212> DNA
<213> Mammalian (Human) PAK4

<400> 27

```
cgttcctggg cttcccgctc cgcaggcctg cggaggactg gcccagcaag gtcccaggtc      60
ttccctctcc ttagcgccta agagagaggc ccagtgcggg tgaggagtcg cgaggaagag     120
gcggaaggcg ccggaaggca ccatgttccg caagaaaaag aagaaacgcc ctgagatctc     180
agcgccacag aacttccagc accgtgtcca cacctccttc gaccccaaag aaggcaagtt     240
tgtgggcctc cccccacaat ggcagaacat cctggacaca ctgcggcgcc ccaagcccgt     300
ggtggaccct tcgcgaatca cacgggtgca gctccagccc atgaagacag tggtgcgggg     360
cagcgcgatg cctgtggatg gctacatctc ggggctgctc aacgacatcc agaagttgtc     420
agtcatcagc tccaacaccc tgcgtggccg cagccccacc agccggcggc gggcacagtc     480
cctggggctg ctgggggatg agcactgggc caccgaccca gacatgtacc tccagagccc     540
ccagtctgag cgcactgacc cccacggcct ctacctcagc tgcaacgggg gcacaccagc     600
aggccacaag cagatgccgt ggcccgagcc acagagccca cgggtcctgc ccaatgggct     660
ggctgcaaag gcacagtccc tgggccccgc cgagtttcag ggtgcctcgc agcgctgtct     720
gcagctgggt gcctgcctgc agagctcccc accaggagcc tcgcccccca cgggcaccaa     780
taggcatgga atgaaggctg ccaagcatgg ctctgaggag gcccggccac agtcctgcct     840
ggtgggctca gccacaggca ggccaggtgg ggaaggcagc cctagcccta agacccggga     900
gagcagcctg aagcgcaggc tattccgaag catgttcctg tccactgctg ccacagcccc     960
tccaagcagc agcaagccag gccctccacc acagagcaag cccaactcct ctttccgacc    1020
gccgcagaaa gacaaccccc caagcctggt ggccaaggcc cagtccttgc cctcggacca    1080
gccggtgggg accttcagcc ctctgaccac ttcggatacc agcagccccc agaagtccct    1140
ccgcacagcc ccggccacag gccagcttcc aggccggtct tccccagcgg gatccccccg    1200
cacctggcac gcccagatca gcaccagcaa cctgtacctg ccccaggacc ccacggttgc    1260
caagggtgcc ctggctggtg aggacacagg tgttgtgaca catgagcagt tcaaggctgc    1320
gctcaggatg gtggtggacc agggtgaccc ccggctgctg ctggacagct acgtgaagat    1380
tggcgagggc tccaccggca tcgtctgctt ggcccgggag aagcactcgg gccgccaggt    1440
ggccgtcaag atgatggacc tcaggaagca gcagcgcagg gagctgctct tcaacgaggt    1500
ggtgatcatg cgggactacc agcacttcaa cgtggtggag atgtacaaga gctacctggt    1560
gggcgaggag ctgtgggtgc tcatggagtt cctgcaggga ggagccctca cagacatcgt    1620
ctcccaagtc aggctgaatg aggagcagat tgccactgtg tgtgaggctg tgctgcaggc    1680
cctggcctac ctgcatgctc agggtgtcat ccaccgggac atcaagagtg actccatcct    1740
gctgaccctc gatggcaggg tgaagctctc ggacttcgga ttctgtgctc agatcagcaa    1800
agacgtccct aagaggaagt ccctggtggg aacccctac tggatggctc ctgaagtgat     1860
ctccaggtct ttgtatgcca ctgaggtgga tatctggtct ctgggcatca tggtgattga    1920
gatggtagat ggggagccac cgtacttcag tgactcccca gtgcaagcca tgaagaggct    1980
ccgggacagc ccccccaccca agctgaaaaa ctctcacaag gtctccccag tgctgcgaga   2040
cttcctggag cggatgctgg tgcgggaccc ccaagagaga gccacagccc aggagctcct    2100
agaccacccc ttcctgctgc agacagggct acctgagtgc ctggtgcccc tgatccagct    2160
ctaccgaaag cagacctcca cctgctgagc ccaccccaag tatgcctgcc acctacgccc    2220
acaggcaggg cacactgggc agccagcctg ccggcaggac ttgcctgcct cctcctctca    2280
gtattctctc caaagattga aatgtgaagc cccagcccca ccctctgccc ttcagcctac    2340
tgggccaggc cggacctgcc ccctcagtgt ctctccctcc cgagtcccca gatggagacc    2400
cctttctaca ggatgacccc ttgatatttg cacagggata tttctaagaa acgcagaggc    2460
cagcgttcct ggcctctgca gccaacacag tagaaaaggc tgctgtggtt ttttaaaggc    2520
agttgtccac tagtgtccta ggccactgca gagggcagac tgctggtctc cacagatacc    2580
```

```
tgctgttctc agctccagct tcaaacctcg agtctcgaga gggccacggg gtggttttta    2640
tgaccggaat cccgcttcct ccctcacgtc tgatgtcctg aaggtgcagt cccacctgta    2700
cagcccctcc ccgccaagaa ctgtgaatgg cctgctccag gccatggctg gggcaggga     2760
gtgaggggac aatttctgag tgaaagagaa agaatggggt cggtggtgaa ggtgctctca    2820
ctttacagaa tggagagaac atcgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg    2880
tgtgtgtgtg tgtgtgtgtg tgtgtgtaag gggaggaaag ccaccttgac agcccaggtc    2940
cctccaggtc acccacagcc agtttcagga aggctgcccc tctctcccac taagttctgg    3000
cctgaaggga cctgctttct tggcctggct tccacctctc cactcctgtg tctacctggc    3060
cagtggagtg gtccatgcta agtctaacac tcctgggagc tcaggaggct tctgagcttc    3120
tcctgtactg tgcatcgtga gggccagaga caggaatgta aggattggca actgtgttac    3180
ctttcaagtt tatctcaata accaggtcat cagggaccca ttgttctctt cagaacccta    3240
tctgggagag aaggcgaacc acctccgggt ttccatcatg tcaaggtcac aggcatccat    3300
gtgtgcaaac catctgcccc agctgcctcc acagactgct gtctccttgt cctcctcggc    3360
cctgccccac ttcagggctg ctgtgagatg gaattccagg aaagaacttc aggtgtctgg    3420
accctttcta tctagataat atttttagat tcttctgctc cctagtgacc tacctggggg    3480
caaagaaatt gcaaggactt ttttttaagg gtcagagttt tcaaaacaaa agcatcttcc    3540
ctagaaattt ttgtgaattg tttgcacttg tgcctgtttt aaattaaatt gagtgttcaa    3600
agcc                                                                 3604
```

<210> 28
<211> 2050
<212> DNA
<213> Mammalian (Human) PAK5

<400> 28

```
ggccagtggg gcgaaactgg cagctggccg gccctttaac acctacccga gggctgacac      60
ggaccaccca tcccggggtg cccaggggga gcctcatgac gtggccccta acgggccatc     120
agcggggggc ctggccatcc cccagtcctc ctcctcctcc tcccggcctc ccacccgagc     180
ccgaggtgcc cccagccctg gagtgctggg accccacgcc tcagagcccc agctggcccc     240
tccagcctgc acccccgccg cccctgctgt tcctgggccc cctggccccc gctcaccaca     300
gcgggagcca cagcgagtat cccatgagca gttccgggct gccctgcagc tggtggtgga     360
cccaggcgac cccgctcct acctggacaa cttcatcaag attggcgagg gctccacggg      420
catcgtgtgc atcgccaccg tgcgcagctc gggcaagctg gtggccgtca agaagatgga     480
cctgcgcaag cagcagaggc gcgagctgct cttcaacgag gtggtaatca tgagggacta     540
ccagcacgag aatgtggtgg agatgtacaa cagctacctg gtgggggacg agctctgggt     600
ggtcatggag ttcctggaag gaggcgccct caccgacatc gtcacccaca ccaggatgaa     660
cgaggagcag atcgcggccg tgtgccttgc agtgctgcag gccctgtcgg tgctccacgc     720
ccagggcgtc atccaccggg acatcaagag cgactcgatc ctgctgaccc atgatggcag     780
ggtgaagctg tcagactttg ggttctgcgc ccaggtgagc aaggaagtgc cccgaaggaa     840
gtcgctggtc ggcacgccct actggatggc cccagagctc atctcccgcc ttccctacgg     900
gccagaggta gacatctggt cgctggggat aatggtgatt gagatggtgg acggagagcc     960
cccctacttc aacgagccac ccctcaaagc catgaagatg attcgggaca acctgccacc    1020
ccgactgaag aacctgcaca aggtgtcgcc atccctgaag ggcttcctgg accgcctgct    1080
ggtgcgagac cctgcccagc gggccacggc agccgagctg ctgaagcacc cattcctggc    1140
caaggcaggg ccgcctgcca gcatcgtgcc cctcatgcgc cagaaccgca ccagatgagg    1200
cccagcgccc ttcccctcaa ccaaagagcc cccccggtc acccccgccc cactgaggcc     1260
agtagggggc caggcctccc actcctccca gcccgggaga tgctccgcgt ggcaccaccc    1320
tccttgctgg gggtagatga gaccctacta ctgaactcca gttttgatct cgtgactttt    1380
agaaaaacac agggactcgt gggagcaagc gaggctccca ggacccccac cctctgggac    1440
aggccctccc ccatgttctt ctgtctccag gaagggcagc ggccctccca tcactggaag    1500
tctgcagtgg gggtcgctgg gggtggagag aacactaaga ggtgaacatg tatgagtgtg    1560
tgcacgcgtg tgagtgtgca tgtgtgtgtg tgtgcaaagg tccagccacc ccgtcctcca    1620
gcccgcaagg ggtgtctggc gccttgcctg acacccagcc ccctctcccc ctgagccatt    1680
```

gtgggggtcg atcatgaatg tccgaagagt ggccttttcc cgtagccctg cgcccccttt 1740
ctgtggctgg atggggagac aggtcagggc cccccaccct ctccagcccc tgcagcaaat 1800
gactactgca cctggacagc ctcctctttt ctagaagtct atttatattg tcattttata 1860
acactctagc ccctgccctt attgggggac agatggtccc tgtcctgcgg ggtggccctg 1920
gcagaaccac tgcctgaaga accaggttcc tgcccggtca gcgcagcccc agcccgccca 1980
cccctgcctc gagttagttt tacaattaaa acattgtctt gttttgtgaa aaaaaaaaaa 2040
aaaaaaaaaa 2050

<210> 29
<211> 681
<212> PRT
<213> Mammalian (Human) PAK4

<400> 29

Met Phe Arg Lys Lys Lys Lys Lys Arg Pro Glu Ile Ser Ala Pro Gln
1 5 10 15

Asn Phe Gln His Arg Val His Thr Ser Phe Asp Pro Lys Glu Gly Lys
20 25 30

Phe Val Gly Leu Pro Pro Gln Trp Gln Asn Ile Leu Asp Thr Leu Arg
35 40 45

Arg Pro Lys Pro Val Val Asp Pro Ser Arg Ile Thr Arg Val Gln Leu
50 55 60

Gln Pro Met Lys Thr Val Val Arg Gly Ser Ala Met Pro Val Asp Gly
65 70 75 80

Tyr Ile Ser Gly Leu Leu Asn Asp Ile Gln Lys Leu Ser Val Ile Ser
85 90 95

Ser Asn Thr Leu Arg Gly Arg Ser Pro Thr Ser Arg Arg Arg Ala Gln
100 105 110

Ser Leu Gly Leu Leu Gly Asp Glu His Trp Ala Thr Asp Pro Asp Met
115 120 125

Tyr Leu Gln Ser Pro Gln Ser Glu Arg Thr Asp Pro His Gly Leu Tyr
130 135 140

Leu Ser Cys Asn Gly Gly Thr Pro Ala Gly His Lys Gln Met Pro Trp
145 150 155 160

Pro Glu Pro Gln Ser Pro Arg Val Leu Pro Asn Gly Leu Ala Ala Lys
165 170 175

Ala Gln Ser Leu Gly Pro Ala Glu Phe Gln Gly Ala Ser Gln Arg Cys
180 185 190

Leu Gln Leu Gly Ala Cys Leu Gln Ser Ser Pro Pro Gly Ala Ser Pro
195 200 205

Pro Thr Gly Thr Asn Arg His Gly Met Lys Ala Ala Lys His Gly Ser
210 215 220

Glu Glu Ala Arg Pro Gln Ser Cys Leu Val Gly Ser Ala Thr Gly Arg
225 230 235 240

Pro Gly Gly Glu Gly Ser Pro Ser Pro Lys Thr Arg Glu Ser Ser Leu
245 250 255

Lys Arg Arg Leu Phe Arg Ser Met Phe Leu Ser Thr Ala Ala Thr Ala
260 265 270

Pro Pro Ser Ser Ser Lys Pro Gly Pro Pro Pro Gln Ser Lys Pro Asn
275 280 285

Ser Ser Phe Arg Pro Pro Gln Lys Asp Asn Pro Pro Ser Leu Val Ala
290 295 300

Lys Ala Gln Ser Leu Pro Ser Asp Gln Pro Val Gly Thr Phe Ser Pro
305 310 315 320

Leu Thr Thr Ser Asp Thr Ser Ser Pro Gln Lys Ser Leu Arg Thr Ala
325 330 335

Pro Ala Thr Gly Gln Leu Pro Gly Arg Ser Ser Pro Ala Gly Ser Pro
340 345 350

Arg Thr Trp His Ala Gln Ile Ser Thr Ser Asn Leu Tyr Leu Pro Gln
355 360 365

Asp Pro Thr Val Ala Lys Gly Ala Leu Ala Gly Glu Asp Thr Gly Val
370 375 380

Val Thr His Glu Gln Phe Lys Ala Ala Leu Arg Met Val Val Asp Gln
385 390 395 400

Gly Asp Pro Arg Leu Leu Leu Asp Ser Tyr Val Lys Ile Gly Glu Gly
405 410 415

Ser Thr Gly Ile Val Cys Leu Ala Arg Glu Lys His Ser Gly Arg Gln
420 425 430

Val Ala Val Lys Met Met Asp Leu Arg Lys Gln Gln Arg Arg Glu Leu
435 440 445

Leu Phe Asn Glu Val Val Ile Met Arg Asp Tyr Gln His Phe Asn Val
450 455 460

Val Glu Met Tyr Lys Ser Tyr Leu Val Gly Glu Glu Leu Trp Val Leu
465 470 475 480

Met Glu Phe Leu Gln Gly Gly Ala Leu Thr Asp Ile Val Ser Gln Val
485 490 495

Arg Leu Asn Glu Glu Gln Ile Ala Thr Val Cys Glu Ala Val Leu Gln
500 505 510

Ala Leu Ala Tyr Leu His Ala Gln Gly Val Ile His Arg Asp Ile Lys
515 520 525

Ser Asp Ser Ile Leu Leu Thr Leu Asp Gly Arg Val Lys Leu Ser Asp
530 535 540

Phe Gly Phe Cys Ala Gln Ile Ser Lys Asp Val Pro Lys Arg Lys Ser
545 550 555 560

Leu Val Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Ile Ser Arg Ser
565 570 575

Leu Tyr Ala Thr Glu Val Asp Ile Trp Ser Leu Gly Ile Met Val Ile
580 585 590

Glu Met Val Asp Gly Glu Pro Pro Tyr Phe Ser Asp Ser Pro Val Gln
595 600 605

Ala Met Lys Arg Leu Arg Asp Ser Pro Pro Pro Lys Leu Lys Asn Ser
610 615 620

His Lys Val Ser Pro Val Leu Arg Asp Phe Leu Glu Arg Met Leu Val
625 630 635 640

Arg Asp Pro Gln Glu Arg Ala Thr Ala Gln Glu Leu Leu Asp His Pro
645 650 655

Phe Leu Leu Gln Thr Gly Leu Pro Glu Cys Leu Val Pro Leu Ile Gln
660 665 670

Leu Tyr Arg Lys Gln Thr Ser Thr Cys
675 680

<210> 30
<211> 398
<212> PRT
<213> Mammalian (Human) PAK5

<400> 30

Ala Ser Gly Ala Lys Leu Ala Ala Gly Arg Pro Phe Asn Thr Tyr Pro
1 5 10 15

Arg Ala Asp Thr Asp His Pro Ser Arg Gly Ala Gln Gly Glu Pro His
20 25 30

Asp Val Ala Pro Asn Gly Pro Ser Ala Gly Gly Leu Ala Ile Pro Gln
35 40 45

Ser Ser Ser Ser Ser Ser Arg Pro Pro Thr Arg Ala Arg Gly Ala Pro
50 55 60

Ser Pro Gly Val Leu Gly Pro His Ala Ser Glu Pro Gln Leu Ala Pro
65 70 75 80

Pro Ala Cys Thr Pro Ala Ala Pro Ala Val Pro Gly Pro Pro Gly Pro
85 90 95

Arg Ser Pro Gln Arg Glu Pro Gln Arg Val Ser His Glu Gln Phe Arg
100 105 110

Ala Ala Leu Gln Leu Val Val Asp Pro Gly Asp Pro Arg Ser Tyr Leu
115 120 125

Asp Asn Phe Ile Lys Ile Gly Glu Gly Ser Thr Gly Ile Val Cys Ile
130 135 140

Ala Thr Val Arg Ser Ser Gly Lys Leu Val Ala Val Lys Lys Met Asp
145 150 155 160

Leu Arg Lys Gln Gln Arg Arg Glu Leu Leu Phe Asn Glu Val Val Ile
165 170 175

Met Arg Asp Tyr Gln His Glu Asn Val Val Glu Met Tyr Asn Ser Tyr
180 185 190

Leu Val Gly Asp Glu Leu Trp Val Val Met Glu Phe Leu Glu Gly Gly
195 200 205

Ala Leu Thr Asp Ile Val Thr His Thr Arg Met Asn Glu Glu Gln Ile
210 215 220

Ala Ala Val Cys Leu Ala Val Leu Gln Ala Leu Ser Val Leu His Ala
225 230 235 240

Gln Gly Val Ile His Arg Asp Ile Lys Ser Asp Ser Ile Leu Leu Thr
245 250 255

His Asp Gly Arg Val Lys Leu Ser Asp Phe Gly Phe Cys Ala Gln Val
260 265 270

Ser Lys Glu Val Pro Arg Arg Lys Ser Leu Val Gly Thr Pro Tyr Trp
275 280 285

Met Ala Pro Glu Leu Ile Ser Arg Leu Pro Tyr Gly Pro Glu Val Asp
290 295 300

Ile Trp Ser Leu Gly Ile Met Val Ile Glu Met Val Asp Gly Glu Pro
305 310 315 320

Pro Tyr Phe Asn Glu Pro Pro Leu Lys Ala Met Lys Met Ile Arg Asp
325 330 335

Asn Leu Pro Pro Arg Leu Lys Asn Leu His Lys Val Ser Pro Ser Leu
340 345 350

Lys Gly Phe Leu Asp Arg Leu Leu Val Arg Asp Pro Ala Gln Arg Ala
355 360 365

Thr Ala Ala Glu Leu Leu Lys His Pro Phe Leu Ala Lys Ala Gly Pro
370 375 380

Pro Ala Ser Ile Val Pro Leu Met Arg Gln Asn Arg Thr Arg
385 390 395

<210> 31
<211> 1001
<212> PRT
<213> Mammalian (murine/human) SULU3

<400> 31

Met Pro Ser Thr Asn Arg Ala Gly Ser Leu Lys Asp Pro Glu Ile Ala
1 5 10 15

Glu Leu Phe Phe Lys Glu Asp Pro Glu Lys Leu Phe Thr Asp Leu Arg
20 25 30

Glu Ile Gly His Gly Ser Phe Gly Ala Val Tyr Phe Ala Arg Asp Val
35 40 45

Arg Thr Asn Glu Val Val Ala Ile Lys Lys Met Ser Tyr Ser Gly Lys
50 55 60

Gln Ser Thr Glu Lys Trp Gln Asp Ile Ile Lys Glu Val Lys Phe Leu
65 70 75 80

Gln Arg Ile Lys His Pro Asn Ser Ile Glu Tyr Lys Gly Cys Tyr Leu
85 90 95

Arg Glu His Thr Ala Trp Leu Val Met Glu Tyr Cys Leu Gly Ser Ala
100 105 110

Ser Asp Leu Leu Glu Val His Lys Lys Pro Leu Gln Glu Val Glu Ile
115 120 125

Ala Ala Ile Thr His Gly Ala Leu Gln Gly Leu Ala Tyr Leu His Ser
130 135 140

His Thr Met Ile His Arg Asp Ile Lys Ala Gly Asn Ile Leu Leu Thr
145 150 155 160

Glu Pro Gly Gln Val Lys Leu Ala Asp Phe Gly Ser Ala Ser Met Ala
165 170 175

Ser Pro Ala Asn Ser Phe Val Gly Thr Pro Tyr Trp Met Ala Pro Glu
180 185 190

Val Ile Leu Ala Met Asp Glu Gly Gln Tyr Asp Gly Lys Val Asp Val
195 200 205

Trp Ser Leu Gly Ile Thr Cys Ile Glu Leu Ala Glu Arg Lys Pro Pro

210 215 220

Leu Phe Asn Met Asn Ala Met Ser Ala Leu Tyr His Ile Ala Gln Asn
225 230 235 240

Glu Ser Pro Thr Leu Gln Ser Asn Glu Trp Ser Asp Tyr Phe Arg Asn
245 250 255

Phe Val Asp Ser Cys Leu Gln Lys Ile Pro Gln Asp Arg Pro Thr Ser
260 265 270

Glu Glu Leu Leu Lys His Ile Phe Val Leu Arg Glu Arg Pro Glu Thr
275 280 285

Val Leu Ile Asp Leu Ile Gln Arg Thr Lys Asp Ala Val Arg Glu Leu
290 295 300

Asp Asn Leu Gln Tyr Arg Lys Met Lys Lys Leu Leu Phe Gln Glu Ala
305 310 315 320

His Asn Gly Pro Ala Val Glu Ala Gln Glu Glu Glu Glu Glu Gln Asp
325 330 335

His Gly Val Gly Arg Thr Gly Thr Val Asn Ser Val Gly Ser Asn Gln
340 345 350

Ser Ile Pro Ser Met Ser Ile Ser Ala Ser Ser Gln Ser Ser Ser Val
355 360 365

Asn Ser Leu Pro Asp Val Ser Asp Asp Lys Ser Glu Leu Asp Met Met
370 375 380

Glu Gly Asp His Thr Val Met Ser Asn Ser Ser Val Ile His Leu Lys
385 390 395 400

Pro Glu Glu Glu Asn Tyr Arg Glu Glu Gly Asp Pro Arg Thr Arg Ala
405 410 415

Ser Asp Pro Gln Ser Pro Pro Gln Val Ser Arg His Lys Ser His Tyr
420 425 430

Arg Asn Arg Glu His Phe Ala Thr Ile Arg Thr Ala Ser Leu Val Thr
435 440 445

Arg Gln Met Gln Glu His Glu Gln Asp Ser Glu Leu Arg Glu Gln Met
450 455 460

Ser Gly Tyr Lys Arg Met Arg Arg Gln His Gln Lys Gln Leu Met Thr
465 470 475 480

Leu Glu Asn Lys Leu Lys Ala Glu Met Asp Glu His Arg Leu Arg Leu
485 490 495

Asp Lys Asp Leu Glu Thr Gln Arg Asn Asn Phe Ala Ala Glu Met Glu
500 505 510

Lys Leu Ile Lys Lys His Gln Ala Ala Met Glu Lys Glu Ala Lys Val
515 520 525

Met Ser Asn Glu Glu Lys Lys Phe Gln Gln His Ile Gln Ala Gln Gln
530 535 540

Lys Lys Glu Leu Asn Ser Phe Leu Glu Ser Gln Lys Arg Glu Tyr Lys
545 550 555 560

Leu Arg Lys Glu Gln Leu Lys Glu Glu Leu Asn Glu Asn Gln Ser Thr
565 570 575

Pro Lys Lys Glu Lys Gln Glu Trp Leu Ser Lys Gln Lys Glu Asn Ile
580 585 590

Gln His Phe Gln Ala Glu Glu Glu Ala Asn Leu Leu Arg Arg Gln Arg
595 600 605

Gln Tyr Leu Glu Leu Glu Cys Arg Arg Phe Lys Arg Arg Met Leu Leu
610 615 620

Gly Arg His Asn Leu Glu Gln Asp Leu Val Arg Glu Glu Leu Asn Lys
625 630 635 640

Arg Gln Thr Gln Lys Asp Leu Glu His Ala Met Leu Leu Arg Gln His
645 650 655

Glu Ser Met Gln Glu Leu Glu Phe Arg His Leu Asn Thr Ile Gln Lys
660 665 670

Met Arg Cys Glu Leu Ile Arg Leu Gln His Gln Thr Glu Leu Thr Asn
675 680 685

Gln Leu Glu Tyr Asn Lys Arg Arg Glu Arg Glu Leu Arg Arg Lys His
690 695 700

Val Met Glu Val Arg Gln Gln Pro Lys Ser Leu Lys Ser Lys Glu Leu
705 710 715 720

Gln Ile Lys Lys Gln Phe Gln Asp Thr Cys Lys Ile Gln Thr Arg Gln
725 730 735

Tyr Lys Ala Leu Arg Asn His Leu Leu Glu Thr Thr Pro Lys Ser Glu
740 745 750

His Lys Ala Val Leu Lys Arg Leu Lys Glu Glu Gln Thr Arg Lys Leu
755 760 765

Ala Ile Leu Ala Glu Gln Tyr Asp His Ser Ile Asn Glu Met Leu Ser
770 775 780

Thr Gln Ala Leu Arg Leu Asp Glu Ala Gln Glu Ala Glu Cys Gln Val
785 790 795 800

Leu Lys Met Gln Leu Gln Gln Glu Leu Glu Leu Leu Asn Ala Tyr Gln

```
                805                 810                 815

Ser Lys Ile Lys Met Gln Ala Glu Ala Gln His Asp Arg Glu Leu Arg
            820                 825                 830

Glu Leu Glu Gln Arg Val Ser Leu Arg Arg Ala Leu Leu Glu Gln Lys
        835                 840                 845

Ile Glu Glu Glu Met Leu Ala Leu Gln Asn Glu Arg Thr Glu Arg Ile
    850                 855                 860

Arg Ser Leu Leu Glu Arg Gln Ala Arg Glu Ile Glu Ala Phe Asp Ser
865                 870                 875                 880

Glu Ser Met Arg Leu Gly Phe Ser Asn Met Val Leu Ser Asn Leu Ser
                885                 890                 895

Pro Glu Ala Phe Ser His Ser Tyr Pro Gly Ala Ser Gly Trp Ser His
            900                 905                 910

Asn Pro Thr Gly Gly Pro Gly Pro His Trp Gly His Pro Met Gly Gly
        915                 920                 925

Pro Pro Gln Ala Trp Gly His Pro Met Gln Gly Gly Pro Gln Pro Trp
    930                 935                 940

Gly His Pro Ser Gly Pro Met Gln Gly Val Pro Arg Gly Ser Ser Met
945                 950                 955                 960

Gly Val Arg Asn Ser Pro Gln Ala Leu Arg Arg Thr Ala Ser Gly Gly
                965                 970                 975

Arg Thr Glu Gln Gly Met Ser Arg Ser Thr Ser Val Thr Ser Gln Ile
            980                 985                 990

Ser Asn Gly Ser His Met Ser Tyr Thr
        995                 1000
```

<210> 32
<211> 25
<212> DNA
<213> TRK1

<220>
<223> "n" stands for a, c, g or t.
"y" stands for c or t.
"r" stands for a or g.

<400> 32

ctgaattcgg ngcnttyggn aargt 25

<210> 33
<211> 24
<212> DNA
<213> TRK4

<220>
<223> "n" stands for a, c, g or t.
"y" stands for c or t.

<400> 33

gctggatccy tcnggnggca tcca 24

<210> 34
<211> 23
<212> DNA
<213> ROS1

<220>
<223> "n" stands for a, c, g or t.
"y" stands for c or t.
"r" stands for a or g.

<400> 34

gcnttyggng argtntayga rgg 23

<210> 35
<211> 24
<212> DNA
<213> CCK4b

<220>
<223> "n" stands for a, c, g or t.
"y" stands for c or t.
"s" stands for c or g.
"w" stands for a or t.

<400> 35

gctggatccy tcnggnswca tcca 24

<210> 36
<211> 23
<212> DNA
<213> CCK4c

<220>
<223> "n" stands for a, c, g or t.
"y" stands for c or t.
"r" stands for a or g.

<400> 36

gagttyggng argtnttyyt ngc 23

<210> 37
<211> 6
<212> PRT
<213> TRK1

<400> 37

Gly Ala Phe Gly Lys Val
1 5

<210> 38
<211> 5
<212> PRT
<213> TRK4

<400> 38

Trp Met Pro Pro Glu
1 5

<210> 39
<211> 8
<212> PRT
<213> ROS1

<400> 39

Ala Phe Gly Glu Val Tyr Glu Gly
1 5

<210> 40
<211> 5
<212> PRT
<213> CCK4b

<400> 40

Trp Met Ser Pro Glu
1 5

<210> 41
<211> 8
<212> PRT
<213> CCK4c

<400> 41

Glu Phe Gly Glu Val Tyr Glu Gly
 1   5

<210> 42
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 42

cacagaaacg gtcagattca c 21

<210> 43
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 43

gatcagggtg acatcaaggg ac 22

<210> 44
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 44

ctcatctgta cacacttcat gg 22

<210> 45
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 45

gattcccaca ctgtagatgt c 21

<210> 46
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 46

ggccctcgac tacatccacc acat 24

<210> 47
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 47

caacgaaact aacacagcat aagg 24

<210> 48
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthesized nucleic acid molecule

<400> 48

atggcgaacg actctcccgc gaa 23

<210> 49
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 49

acaccaaaat caacaagttt cacctc 26

<210> 50
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 50

agttacaagg aattccaagt tct 23

<210> 51
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 51

atgaagagga agaaatcaaa ctg 23

<210> 52
<211> 20

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 52

agatggactg tactgggagg 20

<210> 53
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 53

actttgtgca gctctgtggg 20

<210> 54
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 54

aaggttatgg atgtcacagg g 21

<210> 55
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 55

ctcacaaggt tgccaacagg 20

<210> 56
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 56

agtccccacc agaaggttta c 21

<210> 57
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 57

tcaggggtca gaggtcacg 19

<210> 58
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 58

cccaaaccct accacaaatt c 21

<210> 59
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 59

cccccgggaa acgatgacca 20

<210> 60
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 60

agccgctgcc cctcctctac tgt 23

<210> 61
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 61

accgcaacat cgccacctac tac 23

<210> 62
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 62

ctcgacgtcg tggaccacc 19

<210> 63
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 63

caatgttaac ccactctatg tctc 24

<210> 64
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 64

agtttgccga tgtttttctt ttc 23

<210> 65
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 65

ccgccatgaa ccccggctt 19

<210> 66
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 66

cgattgccaa agaccgtgtc a 21

<210> 67
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 67

agaagttgca gctgttgaga gga 23

<210> 68
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 68

tatggcccgt gtaaggattt c 21

<210> 69
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 69

gtgccagaag tgttgtgttg taa 23

<210> 70
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 70

tattgaattg gcggaacgga ag 22

<210> 71
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 71

ttgttttgtg ctcattcttt ggag 24

<210> 72
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 72

gattgctttg tgctcattct ttgg 24

<210> 73
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 73

ttgttctaag agtgccctcc g 21

<210> 74
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 74

aagaccatgc cgtgcgccg 19

<210> 75
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 75

attccttcag gttctggtta tgg 23

<210> 76
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 76

agtccgccaa gcctcaatg 19

<210> 77
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 77

caccttcagc tgctctatca t 21

<210> 78
<211> 12
<212> PRT
<213> Peptide 540A

<400> 78

His Gly Asp Pro Arg Pro Glu Pro Arg Pro Thr Gln
1 5 10

<210> 79
<211> 10
<212> PRT
<213> Peptide 539A

<400> 79

Cys Leu Asp Phe Pro Lys Glu Asp Tyr Arg
1 5 10

<210> 80
<211> 19
<212> PRT
<213> Peptide 541A

<400> 80

Asp Pro Arg Thr Arg Ala Ser Asp Pro Gln Ser Pro Pro Gln Val Ser
1 5 10 15

Arg His Lys

<210> 81
<211> 14
<212> PRT
<213> Peptide 542A

<400> 81

Pro Ser Thr Asn Arg Ala Gly Ser Leu Lys Asp Pro Glu Cys
1 5 10

<210> 82
<211> 15
<212> PRT
<213> Peptide 554A

<400> 82

Cys Leu Val Pro Leu Ile Gln Leu Tyr Arg Lys Gln Thr Ser Thr
1 5 10 15

<210> 83
<211> 10
<212> PRT
<213> Peptide 579A

<400> 83

Cys Pro Leu Met Arg Gln Asn Arg Thr Arg
1 5 10

<210> 84
<211> 426

<212> PRT
<213> STE20h

<400> 84

Met Ala His Leu Arg Gly Phe Ala Asn Gln His Ser Arg Val Asp Pro
1 5 10 15

Glu Glu Leu Phe Thr Lys Leu Asp Arg Ile Gly Lys Gly Ser Phe Gly
20 25 30

Glu Val Tyr Lys Gly Ile Asp Asn His Thr Lys Glu Val Val Ala Ile
35 40 45

Lys Ile Ile Asp Leu Glu Glu Ala Glu Asp Glu Ile Glu Asp Ile Gln
50 55 60

Gln Glu Ile Thr Val Leu Ser Gln Cys Asp Ser Pro Tyr Ile Thr Arg
65 70 75 80

Tyr Phe Gly Ser Tyr Leu Lys Ser Thr Lys Leu Trp Ile Ile Met Glu
85 90 95

Tyr Leu Gly Gly Gly Ser Ala Leu Asp Leu Leu Lys Pro Gly Pro Leu
100 105 110

Glu Glu Thr Tyr Ile Ala Thr Ile Leu Arg Glu Ile Leu Lys Gly Leu
115 120 125

Asp Tyr Leu His Ser Glu Arg Lys Ile His Arg Asp Ile Lys Ala Ala
130 135 140

Asn Val Leu Leu Ser Glu Gln Gly Asp Val Lys Leu Ala Asp Phe Gly
145 150 155 160

Val Ala Gly Gln Leu Thr Asp Thr Gln Ile Lys Arg Asn Thr Phe Val
165 170 175

Gly Thr Pro Phe Trp Met Ala Pro Glu Val Ile Lys Gln Ser Ala Tyr
180 185 190

Asp Phe Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr Ala Ile Glu Leu
195 200 205

Ala Lys Gly Glu Pro Pro Asn Ser Asp Leu His Pro Met Arg Val Leu
210 215 220

Phe Leu Ile Pro Lys Asn Ser Pro Pro Thr Leu Glu Gly Gln His Ser
225 230 235 240

Lys Pro Phe Lys Glu Phe Val Glu Ala Cys Leu Asn Lys Asp Pro Arg
245 250 255

Phe Arg Pro Thr Ala Lys Glu Leu Leu Lys His Lys Phe Ile Thr Arg
260 265 270

Tyr Thr Lys Lys Thr Ser Phe Leu Thr Glu Leu Ile Asp Arg Tyr Lys
        275   280   285

Arg Trp Lys Ser Glu Gly His Gly Glu Glu Ser Ser Ser Glu Asp Ser
    290   295   300

Asp Ile Asp Gly Glu Ala Glu Asp Gly Glu Gln Gly Pro Ile Trp Thr
305   310   315   320

Phe Pro Pro Thr Ile Arg Pro Ser Pro His Ser Lys Leu His Lys Gly
                325   330   335

Thr Ala Leu His Ser Ser Gln Lys Pro Ala Glu Pro Val Lys Arg Gln
            340   345   350

Pro Arg Ser Gln Cys Leu Ser Thr Leu Val Arg Pro Val Phe Gly Glu
        355   360   365

Leu Lys Glu Lys His Lys Gln Ser Gly Gly Ser Val Gly Ala Leu Glu
    370   375   380

Glu Leu Glu Asn Ala Phe Ser Leu Ala Glu Glu Ser Cys Pro Gly Ile
385   390   395   400

Ser Asp Lys Leu Met Val His Leu Val Glu Arg Val Gln Arg Phe Ser
                405   410   415

His Asn Arg Asn His Leu Thr Ser Thr Arg
            420   425

<210> 85
<211> 431
<212> PRT
<213> MST3

<400> 85

Met Ala His Ser Pro Val Gln Ser Gly Leu Pro Gly Met Gln Asn Leu
1   5   10   15

Lys Ala Asp Pro Glu Glu Leu Phe Thr Lys Leu Glu Lys Ile Gly Lys
            20   25   30

Gly Ser Phe Gly Glu Val Phe Lys Gly Ile Asp Asn Arg Thr Gln Lys
        35   40   45

Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala Glu Asp Glu Ile
    50   55   60

Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser Gln Cys Asp Ser Pro
65   70   75   80

Tyr Val Thr Lys Tyr Tyr Gly Ser Tyr Leu Lys Asp Thr Lys Leu Trp

85 90 95

Ile Ile Met Glu Tyr Leu Gly Gly Gly Ser Ala Leu Asp Leu Leu Glu
100 105 110

Pro Gly Pro Leu Asp Glu Thr Gln Ile Ala Thr Ile Leu Arg Glu Ile
115 120 125

Leu Lys Gly Leu Asp Tyr Leu His Ser Glu Lys Lys Ile His Arg Asp
130 135 140

Ile Lys Ala Ala Asn Val Leu Leu Ser Glu His Gly Glu Val Lys Leu
145 150 155 160

Ala Asp Phe Gly Val Ala Gly Gln Leu Thr Asp Thr Gln Ile Lys Arg
165 170 175

Asn Thr Phe Val Gly Thr Pro Phe Trp Met Ala Pro Glu Val Ile Lys
180 185 190

Gln Ser Ala Tyr Asp Ser Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr
195 200 205

Ala Ile Glu Leu Ala Arg Gly Glu Pro Pro His Ser Glu Leu His Pro
210 215 220

Met Lys Val Leu Phe Leu Ile Pro Lys Asn Asn Pro Pro Thr Leu Glu
225 230 235 240

Gly Asn Tyr Ser Lys Pro Leu Lys Glu Phe Val Glu Ala Cys Leu Asn
245 250 255

Lys Glu Pro Ser Phe Arg Pro Thr Ala Lys Glu Leu Leu Lys His Lys
260 265 270

Phe Ile Leu Arg Asn Ala Lys Lys Thr Ser Tyr Leu Thr Glu Leu Ile
275 280 285

Asp Arg Tyr Lys Arg Trp Lys Ala Glu Gln Ser His Asp Asp Ser Ser
290 295 300

Ser Glu Asp Ser Asp Ala Glu Thr Asp Gly Gln Ala Ser Gly Gly Ser
305 310 315 320

Asp Ser Gly Asp Trp Ile Phe Thr Ile Arg Glu Lys Asp Pro Lys Asn
325 330 335

Leu Glu Asn Gly Ala Leu Gln Pro Ser Asp Leu Asp Arg Asn Lys Met
340 345 350

Lys Asp Ile Pro Lys Arg Pro Phe Ser Gln Cys Leu Ser Thr Ile Ile
355 360 365

Ser Pro Leu Phe Ala Glu Leu Lys Glu Lys Ser Gln Ala Cys Gly Gly
370 375 380

Asn Leu Gly Ser Ile Glu Glu Leu Arg Gly Ala Ile Tyr Leu Ala Glu
385 390 395 400

Glu Ala Cys Pro Gly Ile Ser Asp Thr Met Val Ala Gln Leu Val Gln
405 410 415

Arg Leu Gln Arg Tyr Ser Leu Ser Gly Gly Gly Thr Ser Ser His
420 425 430

<210> 86
<211> 443
<212> PRT
<213> T19A5.2_ce

<220>
<223> "Xaa" stands for any amino acid.

<400> 86

Met Thr Thr Thr Ser Ser Asp Glu Leu Pro Arg Gln Ala Asp Asp Asp
1 5 10 15

Ser Met Lys Trp Asp Arg Ile Tyr Ile Gln Lys Leu Asp Pro Glu Val
20 25 30

Ile Phe Thr Lys Gln Glu Arg Ile Gly Arg Gly Ser Phe Gly Glu Val
35 40 45

Tyr Lys Gly Ile Asp Asn Arg Thr Gly Arg Val Val Ala Ile Lys Ile
50 55 60

Ile Asp Leu Glu Gln Ala Glu Asp Glu Ile Glu Asp Ile Gln Gln Glu
65 70 75 80

Ile Gln Val Leu Ser Gln Cys Asp Ser Gln Tyr Val Thr Lys Tyr Phe
85 90 95

Gly Ser Phe Leu Lys Gly Ser Lys Leu Trp Ile Ile Met Glu Tyr Leu
100 105 110

Gly Gly Gly Ser Ala Leu Asp Leu Thr Lys Ser Gly Lys Leu Asp Glu
115 120 125

Ser His Ile Ala Val Ile Leu Arg Glu Ile Leu Lys Gly Leu Glu Tyr
130 135 140

Leu His Ser Glu Arg Lys Ile His Arg Asp Ile Lys Ala Ala Asn Val
145 150 155 160

Leu Val Ser Glu His Gly Asp Val Lys Val Ala Asp Phe Gly Val Ala
165 170 175

```
Gly Gln Leu Thr Glu Thr Val Lys Lys Arg Ile Thr Phe Val Gly Ser
            180                 185                 190

Pro Phe Trp Met Ala Pro Glu Leu Ile Lys Gln Ser Ser Tyr Asp Tyr
        195                 200                 205

Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr Ala Ile Glu Leu Ala Asn
    210                 215                 220

Gly Glu Pro Pro His Ser Asp Leu His Pro Met Arg Val Leu Phe Leu
225                 230                 235                 240

Ile Pro Lys Asn Pro Pro Pro Val Leu Gln Gly Ser Gln Trp Ser Lys
                245                 250                 255

Pro Phe Lys Glu Phe Val Glu Met Cys Leu Asn Lys Asp Pro Glu Asn
            260                 265                 270

Arg Pro Ser Ala Ser Thr Leu Leu Lys His Gln Phe Ile Lys Arg Ala
        275                 280                 285

Lys Lys Asn Ser Ile Leu Val Asp Leu Ile Glu Arg Ala Ala Glu Tyr
    290                 295                 300

Arg Leu Arg Thr Gly Val Ser Ser Asp Ser Asp Leu Asp Glu Asp Ser
305                 310                 315                 320

Asp Gly Gly Gly Gly Thr Ser Lys Trp Asp Tyr Pro Thr Val Arg Gly
                325                 330                 335

Pro Arg Val Ser Ala Asp Asp Asp Gly Thr Val Arg Gln Arg Thr Asp
            340                 345                 350

Arg Pro Arg Ala Gln Val Asp Arg Arg Ser Pro Ser Gly Ser Pro Gly
        355                 360                 365

Gly Thr Ile Val Arg Gly Ser Pro Gln Val Ala Ala Val Ala Glu Gln
    370                 375                 380


Leu Arg Asn Ser Xaa Xaa Ala Leu Asp Gln Leu Arg His Val Phe Arg
385                 390                 395                 400

Asp Val Glu Asp Ser Cys Pro Gly Ile Cys Asn Glu Leu Ile Glu Glu
                405                 410                 415

Leu Met Gln Arg Ile Ala Val Pro Gln Val Ser Gln Ser Asp Leu Asp
            420                 425                 430

Ala Ala Ile Arg Arg Leu Thr Thr Pro Pro Ser
        435                 440
```

<210> 87

<211> 275
<212> PRT
<213> Pak_sp

<400> 87

Leu Leu Tyr Arg Asn Phe Val Lys Ile Gly Gln Gly Ala Ser Gly Asp
1 5 10 15

Val Tyr Ser Ala Arg Gln Val Gly Thr Asn Leu Ser Val Ala Ile Lys
20 25 30

Lys Met Asn Ile Asn Gln Gln Pro Lys Lys Glu Phe Ile Val Asn Glu
35 40 45

Ile Leu Val Met Lys Ser His His His Lys Asn Ile Val Asn Phe Ile
50 55 60

Asp Thr Phe Phe Tyr Lys Ser Glu Leu Trp Met Val Met Glu Tyr Met
65 70 75 80

Arg Gly Gly Ser Leu Thr Glu Val Val Thr Asn Asn Thr Leu Ser Glu
85 90 95

Gly Gln Ile Ala Ala Ile Cys Lys Glu Thr Leu Glu Gly Leu Gln His
100 105 110

Leu His Glu Asn Gly Ile Val His Arg Asp Ile Lys Ser Asp Asn Ile
115 120 125

Leu Leu Ser Leu Gln Gly Asp Ile Lys Leu Thr Asp Phe Gly Phe Cys
130 135 140

Ala Gln Ile Asp Ser Asn Met Thr Lys Arg Thr Thr Met Val Gly Thr
145 150 155 160

Pro Tyr Trp Met Ala Pro Glu Val Val Thr Arg Lys Glu Tyr Gly Phe
165 170 175

Lys Val Asp Val Trp Ser Leu Gly Ile Met Ala Ile Glu Met Val Glu
180 185 190

Gly Glu Pro Pro Tyr Leu Asn Glu Asn Pro Leu Arg Ala Leu Tyr Leu
195 200 205

Ile Ala Thr Ile Gly Thr Pro Lys Ile Ser Arg Pro Glu Leu Leu Ser
210 215 220

Ser Val Phe His Asp Phe Leu Ser Lys Ser Leu Thr Val Asn Pro Lys
225 230 235 240

Gln Arg Pro Ser Ser Gly Glu Leu Leu Arg His Pro Phe Leu Lys Gln
245 250 255

Ala Val Pro Val Ser Ser Leu Ile Pro Leu Ile Lys Ser Ile His His
260 265 270

Ser Gly Lys
275

<210> 88
<211> 1109
<212> PRT
<213> ZC504.4_ce

<400> 88

Met Ser Ser Ser Gly Leu Asp Glu Ile Asp Leu Asn Ser Leu Arg Asp
1 5 10 15

Pro Ala Gly Ile Phe Glu Leu Ile Glu Val Val Gly Asn Gly Thr Tyr
20 25 30

Gly Gln Val Tyr Lys Gly Arg His Val Lys Thr Ala Gln Leu Ala Ala
35 40 45

Ile Lys Ile Met Asn Ile Asn Glu Asp Glu Glu Asp Glu Ile Lys Leu
50 55 60

Glu Ile Asn Met Leu Lys Lys His Ser His His Arg Asn Val Ala Thr
65 70 75 80

Tyr Tyr Gly Ala Phe Ile Lys Lys Leu Pro Ser Ser Thr Gly Lys His
85 90 95

Asp Gln Leu Trp Leu Val Met Glu Phe Cys Gly Ser Gly Ser Ile Thr
100 105 110

Asp Leu Val Lys Asn Thr Lys Gly Gly Ser Leu Lys Glu Glu Trp Ile
115 120 125

Ala Tyr Ile Cys Arg Glu Ile Leu Arg Gly Leu Tyr His Leu His Gln
130 135 140

Ser Lys Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu Leu Thr
145 150 155 160

Asp Ser Ala Glu Val Lys Leu Val Asp Phe Gly Val Ser Ala Gln Leu
165 170 175

Asp Lys Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp
180 185 190

Met Ala Pro Glu Val Ile Ala Cys Asp Glu Ser Pro Glu Ala Thr Tyr
195 200 205

Asp Ser Arg Ser Asp Leu Trp Ser Leu Gly Ile Thr Ala Leu Glu Met
210 215 220

Ala Glu Gly His Pro Pro Leu Cys Asp Met His Pro Met Arg Ala Leu
225 230 235 240

Phe Leu Ile Pro Arg Asn Pro Pro Pro Lys Leu Lys Arg Asn Lys Lys
245 250 255

Trp Thr Lys Lys Phe Glu Thr Phe Ile Glu Thr Val Leu Val Lys Asp
260 265 270

Tyr His Gln Arg Pro Tyr Thr Gly Ala Leu Leu Arg His Pro Phe Ile
275 280 285

Lys Glu Gln Pro His Glu Gln Thr Ile Arg His Ser Ile Lys Glu His
290 295 300

Ile Asp Arg Asn Arg Arg Val Lys Lys Asp Asp Ala Asp Tyr Glu Tyr
305 310 315 320

Ser Gly Ser Glu Asp Asp Glu Pro Ser Pro Asn Asn Arg Asp Asp Ser
325 330 335

Glu Ser Ser Ser Met Ile Pro Met Asp Asn Thr Leu Arg Lys Gly Phe
340 345 350

Gln Lys Leu Gln Glu Ser Ser Arg Gly Phe Ala Glu Pro Gly Ala Gln
355 360 365

Gln Leu Arg Arg Leu Pro Gln Gln Pro Ala Pro Ala Pro Phe Gln Tyr
370 375 380

Gln Gln Ser Arg Tyr Val Glu Pro Arg Arg Glu Ser Ser Glu Val Lys
385 390 395 400

Leu Arg Ala Val Ser Ser Arg Gly Ala Ala Asp Gly Pro Arg His Ser
405 410 415

Pro Ala Ser Arg Pro Arg Pro Arg Ser Pro Gln Gln Ser His Pro Ala
420 425 430

Ala Pro His Leu Ala Asp Leu Ala Asn Tyr Glu Lys Arg Arg Arg Ser
435 440 445

Glu Arg Glu Glu Arg Arg Glu Arg Glu Arg Gln Ala His His Ala Met
450 455 460

Pro Ile Ala Arg Val Ser Ala Ser Val Pro Ala Pro Gln Gln Ser Arg
465 470 475 480

Lys Met Ser Glu Pro Leu Leu Ile Thr His Val Lys Pro Glu Asp Leu
485 490 495

Asp Val Leu Ala Ser Glu Leu Ser Lys Met Gly Gly His His Asn Gly
500 505 510

Arg Ser Arg Glu Glu Ser Met Ser Pro Pro Pro Pro Ala Pro Pro Pro

515 520 525

Arg Glu Ala Ser Ile Ser Ser Ile Thr Asp Thr Ile Asp Val Gly Glu
530 535 540

Leu Asp Asn Gly Ala Asp Ala Glu Trp Asp Asp Leu Lys Asp Ile Met
545 550 555 560

Met Asn Gly Glu Gly Thr Leu Arg Gly Pro Asn Lys Pro Leu Pro Pro
565 570 575

Thr Pro Thr Asp Gly Glu Asn Thr Leu Val Ser Asp Val Arg Arg Asn
580 585 590

Gly Asn Gly Asn Ser Gly His Gly Ala Tyr Lys Gly Lys Lys Ile Pro
595 600 605

Glu Ile Arg Pro Gly Ile Ile Ser Leu Asp Asp Asp Asp Ser Asp Ser
610 615 620

Asp Asn Glu Glu Gly Asn Glu Pro Leu Met Phe Lys Pro Ile Val Arg
625 630 635 640

Cys Pro Phe Ser Ile Phe Phe Trp Phe Leu Ser Ala Asn Val Ile His
645 650 655

Ser Val Asp Gly Ser Ile Pro Leu Val Lys His Leu Ile Trp Phe Gln
660 665 670

Asn Ala Ser Ser Ser Arg Gly Ala Leu Pro Asp Leu Leu Pro Lys Ser
675 680 685

Pro Asp Leu Arg Arg Gln Ile Asn Asp Gln Thr Arg Gln Met Ser Asp
690 695 700

Asp Arg Ala Asp Glu Gln Pro Asn Gly Phe Gln Asn Ser Asp Ser Arg
705 710 715 720

Ser Ser Ile Gln His Ser Phe Ser Asn Arg Asp Arg Glu Lys Ser Phe
725 730 735

Val Gly Tyr Phe Gly Gly Gly Ala Gly Ala Gly Gly Gly Thr Val Asn
740 745 750

Arg Pro Gly Arg Pro Gln Asp Ile Asn Gln Val Gln Val Asn Val Thr
755 760 765

Pro Asn Ser Asn Gly Thr Pro Ala Glu Asn Asp Ala Pro Glu Ile Arg
770 775 780

Lys Tyr Lys Lys Lys Phe Ser Gly Glu Ile Leu Cys Ala Ala Leu Trp
785 790 795 800

Gly Val Asn Leu Leu Ile Gly Thr Asp Ser Gly Leu Met Leu Leu Asp
805 810 815

Arg Ser Gly Gln Gly Lys Val Tyr Pro Leu Ile Ser Arg Arg Arg Phe
820 825 830

Asp Gln Met Thr Val Leu Glu Gly Gln Asn Ile Leu Ala Thr Ile Ser
835 840 845

Gly Arg Lys Arg Arg Ile Arg Val Tyr Tyr Leu Ser Trp Leu Arg Gln
850 855 860

Lys Ile Leu Arg Thr Glu Gly Ala Gly Ser Ala Asn Thr Thr Glu Lys
865 870 875 880

Arg Asn Gly Trp Val Asn Val Gly Asp Leu Gln Gly Ala Ile His Phe
885 890 895

Lys Ile Val Arg Tyr Glu Arg Ile Lys Phe Leu Val Val Gly Leu Glu
900 905 910

Ser Ser Ile Glu Ile Tyr Ala Trp Ala Pro Lys Pro Tyr His Lys Phe
915 920 925

Met Ser Phe Lys Ser Phe Gly Ser Leu Ser His Val Pro Leu Ile Val
930 935 940

Asp Leu Thr Val Glu Asp Asn Ala Arg Leu Lys Val Leu Tyr Gly Ser
945 950 955 960

Thr Gly Gly Phe His Ala Ile Asp Leu Asp Ser Ala Ala Val Tyr Asp
965 970 975

Ile Tyr Thr Pro Ala Gln Ser Gly Gln Thr Thr Thr Pro His Cys Ile
980 985 990

Val Val Leu Pro Asn Ser Asn Gly Met Gln Leu Leu Leu Cys Tyr Asp
995 1000 1005

Asn Glu Gly Val Tyr Val Asn Thr Tyr Gly Arg Met Thr Lys Asn Val
1010 1015 1020

Val Leu Gln Trp Gly Glu Met Pro Ser Ser Val Ala Tyr Ile Ser Thr
1025 1030 1035 1040

Gly Gln Ile Met Gly Trp Gly Asn Lys Ala Ile Glu Ile Arg Ser Val
1045 1050 1055

Asp Thr Gly His Leu Asp Gly Val Phe Met His Lys Lys Ala Gln Lys
1060 1065 1070

Leu Lys Phe Leu Cys Glu Arg Asn Asp Lys Val Phe Phe Ser Ser Ala
1075 1080 1085

Lys Gly Gly Gly Ser Cys Gln Ile Tyr Phe Met Thr Leu Asn Lys Pro
1090 1095 1100

Gly Leu Thr Asn Trp
1105

<210> 89
<211> 1233
<212> PRT
<213> NIK_m

<400> 89

Met Ala Asn Asp Ser Pro Ala Lys Ser Leu Val Asp Ile Asp Leu Ser
1 5 10 15

Ser Leu Arg Asp Pro Ala Gly Ile Phe Glu Leu Val Glu Val Val Gly
20 25 30

Asn Gly Thr Tyr Gly Gln Val Tyr Lys Gly Arg His Val Lys Thr Val
35 40 45

Thr Ala Ala Ile Lys Val Met Asp Val Thr Glu Asp Glu Glu Glu Glu
50 55 60

Ile Thr Leu Glu Ile Asn Met Leu Lys Lys Tyr Ser His His Arg Asn
65 70 75 80

Ile Ala Thr Tyr Tyr Gly Ala Phe Ile Lys Lys Ser Pro Pro Gly His
85 90 95

Asp Asp Gln Leu Trp Leu Val Met Glu Phe Cys Gly Ala Gly Ser Ile
100 105 110

Thr Asp Leu Val Lys Asn Thr Lys Gly Asn Thr Leu Lys Glu Asp Trp
115 120 125

Ile Ala Tyr Ile Ser Arg Glu Ile Leu Arg Gly Leu Ala His Leu His
130 135 140

Ile His His Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu Leu
145 150 155 160

Thr Glu Asn Ala Glu Val Lys Leu Val Asp Phe Gly Val Ser Ala Gln
165 170 175

Leu Asp Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr
180 185 190

Trp Met Ala Pro Glu Val Ile Ala Cys Asp Glu Asn Pro Asp Ala Thr
195 200 205

Tyr Asp Tyr Arg Ser Asp Leu Trp Ser Cys Gly Ile Thr Ala Ile Glu
210 215 220

Met Ala Glu Gly Gly Pro Pro Leu Cys Asp Met His Pro Met Arg Ala

225 230 235 240

Leu Phe Leu Ile Pro Arg Asn Pro Pro Pro Arg Leu Lys Ser Lys Lys
245 250 255

Trp Ser Lys Lys Phe Phe Ser Phe Ile Glu Gly Cys Leu Val Lys Asn
260 265 270

Tyr Met Gln Arg Pro Ser Thr Glu Gln Leu Leu Lys His Pro Phe Ile
275 280 285

Arg Asp Gln Pro Asn Glu Arg Gln Val Arg Ile Gln Leu Lys Asp His
290 295 300

Ile Asp Arg Thr Arg Lys Lys Arg Gly Glu Lys Asp Glu Thr Glu Tyr
305 310 315 320

Glu Tyr Ser Gly Ser Glu Glu Glu Glu Glu Glu Val Pro Glu Gln Glu
325 330 335

Gly Glu Pro Ser Ser Ile Val Asn Val Pro Gly Glu Ser Thr Leu Arg
340 345 350

Arg Asp Phe Leu Arg Leu Gln Gln Glu Asn Lys Glu Arg Ser Glu Ala
355 360 365

Leu Arg Arg Gln Gln Leu Leu Gln Glu Gln Gln Leu Arg Glu Gln Glu
370 375 380

Glu Tyr Lys Arg Gln Leu Leu Ala Glu Arg Gln Lys Arg Ile Glu Gln
385 390 395 400

Gln Lys Glu Gln Arg Arg Arg Leu Glu Glu Gln Gln Arg Arg Glu Arg
405 410 415

Glu Ala Arg Arg Gln Gln Glu Arg Glu Gln Arg Arg Arg Glu Gln Glu
420 425 430

Glu Lys Arg Arg Leu Glu Glu Leu Glu Arg Arg Arg Lys Glu Glu Glu
435 440 445

Glu Arg Arg Arg Ala Glu Glu Glu Lys Arg Arg Val Glu Arg Glu Gln
450 455 460

Glu Tyr Ile Arg Arg Gln Leu Glu Glu Glu Gln Arg His Leu Glu Ile
465 470 475 480

Leu Gln Gln Gln Leu Leu Gln Glu Gln Ala Met Leu Leu His Asp His
485 490 495

Arg Arg Pro His Ala Gln Gln Gln Pro Pro Pro Pro Gln Gln Gln Asp
500 505 510

Arg Ser Lys Pro Ser Phe His Ala Pro Glu Pro Lys Pro His Tyr Asp
515 520 525

Pro Ala Asp Arg Ala Arg Glu Val Gln Trp Ser His Leu Ala Ser Leu
530 535 540

Lys Asn Asn Val Ser Pro Val Ser Arg Ser His Ser Phe Ser Asp Pro
545 550 555 560

Ser Pro Lys Phe Ala His His His Leu Arg Ser Gln Asp Pro Cys Pro
565 570 575

Pro Ser Arg Ser Glu Gly Leu Ser Gln Ser Ser Asp Ser Lys Ser Glu
580 585 590

Val Pro Glu Pro Thr Gln Lys Ala Trp Ser Arg Ser Asp Ser Asp Glu
595 600 605

Val Pro Pro Arg Val Pro Val Arg Thr Thr Ser Arg Ser Pro Val Leu
610 615 620

Ser Arg Arg Asp Ser Pro Leu Gln Gly Gly Gly Gln Gln Asn Ser Gln
625 630 635 640

Ala Gly Gln Arg Asn Ser Thr Ser Ser Ile Glu Pro Arg Leu Leu Trp
645 650 655

Glu Arg Val Glu Lys Leu Val Pro Arg Pro Gly Ser Gly Ser Ser Ser
660 665 670

Gly Ser Ser Asn Ser Gly Ser Gln Pro Gly Ser His Pro Gly Ser Gln
675 680 685

Ser Gly Ser Gly Glu Arg Phe Arg Val Arg Ser Ser Ser Lys Ser Glu
690 695 700

Gly Ser Pro Ser Pro Arg Gln Glu Ser Ala Ala Lys Lys Pro Asp Asp
705 710 715 720

Lys Lys Glu Val Phe Arg Ser Leu Lys Pro Ala Gly Glu Val Asp Leu
725 730 735

Thr Ala Leu Ala Lys Glu Leu Arg Ala Val Glu Asp Val Arg Pro Pro
740 745 750

His Lys Val Thr Asp Tyr Ser Ser Ser Ser Glu Glu Ser Gly Thr Thr
755 760 765

Asp Glu Glu Glu Glu Asp Val Glu Gln Glu Gly Ala Asp Asp Ser Thr
770 775 780

Ser Gly Pro Glu Asp Thr Arg Ala Ala Ser Ser Pro Asn Leu Ser Asn
785 790 795 800

Gly Glu Thr Glu Ser Val Lys Thr Met Ile Val His Asp Asp Val Glu
805 810 815

Ser Glu Pro Ala Met Thr Pro Ser Lys Glu Gly Thr Leu Ile Val Arg
820 825 830

Gln Thr Gln Ser Ala Ser Ser Thr Leu Gln Lys His Lys Ser Ser Ser
835 840 845

Ser Phe Thr Pro Phe Ile Asp Pro Arg Leu Leu Gln Ile Ser Pro Ser
850 855 860

Ser Gly Thr Thr Val Thr Ser Val Val Gly Phe Ser Cys Asp Gly Leu
865 870 875 880

Arg Pro Glu Ala Ile Arg Gln Asp Pro Thr Arg Lys Gly Ser Val Val
885 890 895

Asn Val Asn Pro Thr Asn Thr Arg Pro Gln Ser Asp Thr Pro Glu Ile
900 905 910

Arg Lys Tyr Lys Lys Arg Phe Asn Ser Glu Ile Leu Cys Ala Ala Leu
915 920 925

Trp Gly Val Asn Leu Leu Val Gly Thr Glu Ser Gly Leu Met Leu Leu
930 935 940

Asp Arg Ser Gly Gln Gly Lys Val Tyr Pro Leu Ile Ser Arg Arg Arg
945 950 955 960

Phe Gln Gln Met Asp Val Leu Glu Gly Leu Asn Val Leu Val Thr Ile
965 970 975

Ser Gly Lys Lys Asp Lys Leu Arg Val Tyr Tyr Leu Ser Trp Leu Arg
980 985 990

Asn Lys Ile Leu His Asn Asp Pro Glu Val Glu Lys Lys Gln Gly Trp
995 1000 1005

Thr Thr Val Gly Asp Leu Glu Gly Cys Val His Tyr Lys Val Val Lys
1010 1015 1020

Tyr Glu Arg Ile Lys Phe Leu Val Ile Ala Leu Lys Ser Ser Val Glu
1025 1030 1035 1040

Val Tyr Ala Trp Ala Pro Lys Pro Tyr His Lys Phe Met Ala Phe Lys
1045 1050 1055

Ser Phe Gly Glu Leu Leu His Lys Pro Leu Leu Val Asp Leu Thr Val
1060 1065 1070

Glu Glu Gly Gln Arg Leu Lys Val Ile Tyr Gly Ser Cys Ala Gly Phe
1075 1080 1085

His Ala Val Asp Val Asp Ser Gly Ser Val Tyr Asp Ile Tyr Leu Pro
1090 1095 1100

Thr His Ile Gln Cys Ser Ile Lys Pro His Ala Ile Ile Ile Leu Pro
1105 1110 1115 1120

Asn Thr Asp Gly Met Glu Leu Leu Val Cys Tyr Glu Asp Glu Gly Val
1125 1130 1135

Tyr Val Asn Thr Tyr Gly Arg Ile Thr Lys Asp Val Val Leu Gln Trp
1140 1145 1150

Gly Glu Met Pro Thr Ser Val Ala Tyr Ile Arg Ser Asn Gln Thr Met
1155 1160 1165

Gly Trp Gly Glu Lys Ala Ile Glu Ile Arg Ser Val Glu Thr Gly His
1170 1175 1180

Leu Asp Gly Val Phe Met His Lys Arg Ala Gln Arg Leu Lys Phe Leu
1185 1190 1195 1200

Cys Gly Arg Asn Asp Lys Val Phe Phe Ser Ser Val Arg Ser Gly Gly
1205 1210 1215

Ser Ser Gln Val Tyr Phe Met Thr Leu Gly Arg Thr Ser Leu Leu Ser
1220 1225 1230

Trp

<210> 90
<211> 982
<212> PRT
<213> SULU_ce

<400> 90

Met Ala Pro Ala Val Leu Asp Lys Pro Gly Val Ile Lys Asp Pro Ser
1 5 10 15

Ile Ala Ala Leu Phe Ser Asn Lys Asp Pro Glu Gln Arg Tyr Gln Asp
20 25 30

Leu Arg Glu Ile Gly His Gly Ser Phe Gly Ala Val Tyr Phe Ala Tyr
35 40 45

Asp Lys Lys Asn Glu Gln Thr Val Ala Ile Lys Lys Met Asn Phe Ser
50 55 60

Gly Lys Gln Ala Val Glu Lys Trp Asn Asp Ile Leu Lys Glu Val Ser
65 70 75 80

Phe Leu Asn Thr Val Val His Pro His Ile Val Asp Tyr Lys Ala Cys
85 90 95

Phe Leu Lys Asp Thr Thr Cys Trp Leu Val Met Glu Tyr Cys Ile Gly
100 105 110

Ser Ala Ala Asp Ile Val Asp Val Leu Arg Lys Gly Met Arg Glu Val
115 120 125

Glu Ile Ala Ala Ile Cys Ser Gln Thr Leu Asp Ala Leu Arg Tyr Leu
130 135 140

His Ser Leu Lys Arg Ile His Arg Asp Ile Lys Ala Gly Asn Ile Leu
145 150 155 160

Leu Ser Asp His Ala Ile Val Lys Leu Ala Asp Phe Gly Ser Ala Ser
165 170 175

Leu Val Asp Pro Ala Gln Thr Phe Ile Gly Thr Pro Phe Phe Met Ala
180 185 190

Pro Glu Val Ile Leu Ala Met Asp Glu Gly His Tyr Thr Asp Arg Ala
195 200 205

Asp Ile Trp Ser Leu Gly Ile Thr Cys Ile Glu Leu Ala Glu Arg Arg
210 215 220

Pro Pro Leu Phe Ser Met Asn Ala Met Ser Ala Leu Tyr His Ile Ala
225 230 235 240

Gln Asn Asp Pro Pro Thr Leu Ser Pro Ile Asp Thr Ser Glu Gln Pro
245 250 255

Glu Trp Ser Leu Glu Phe Val Gln Phe Ile Asp Lys Cys Leu Arg Lys
260 265 270

Pro Ala Glu Glu Arg Met Ser Ala Glu Glu Cys Phe Arg His Pro Phe
275 280 285

Ile Gln Arg Ser Arg Pro Ser Asp Thr Ile Gln Glu Leu Ile Gln Arg
290 295 300

Thr Lys Asn Met Val Leu Glu Leu Asp Asn Phe Gln Tyr Lys Lys Met
305 310 315 320

Arg Lys Leu Met Tyr Leu Asp Glu Thr Glu Gly Lys Glu Gly Ser Glu
325 330 335

Gly Asn Gly Ala Ser Asp Asp Leu Asp Phe His Gly Asn Glu Ala Asn
340 345 350

Ser Ile Gly Arg Ala Gly Asp Ser Ala Ser Ser Arg Ser Ala Ser Leu
355 360 365

Thr Ser Phe Arg Ser Met Gln Ser Ser Gly Gly Ala Gly Leu Leu Val
370 375 380

Ser Thr Asn Thr Thr Gly Ala Met Asp Asn Val His Gly Ser Ser Gly
385 390 395 400

Tyr Gly Asn Gly Ser Ser Ser Thr Thr Ser Ser Ala Arg Arg Arg Pro
405 410 415

Pro Ile Pro Ser Gln Met Leu Ser Ser Thr Ser Thr Ser Gly Val Gly
420 425 430

Thr Met Pro Ser His Gly Ser Val Gly Ala Ser Ile Thr Ala Ile Ala
435 440 445

Val Asn Pro Thr Pro Ser Pro Ser Glu Pro Ile Pro Thr Ser Gln Pro
450 455 460

Thr Ser Lys Ser Glu Ser Ser Ser Ile Leu Glu Thr Ala His Asp Asp
465 470 475 480

Pro Leu Asp Thr Ser Ile Arg Ala Pro Val Lys Asp Leu His Met Pro
485 490 495

His Arg Ala Val Lys Glu Arg Ile Ala Thr Leu Gln Asn His Lys Phe
500 505 510

Ala Thr Leu Arg Ser Gln Arg Ile Ile Asn Gln Glu Gln Glu Glu Tyr
515 520 525

Thr Lys Glu Asn Asn Met Tyr Glu Gln Met Ser Lys Tyr Lys His Leu
530 535 540

Arg Gln Ala His His Lys Glu Leu Gln Gln Phe Glu Glu Arg Cys Ala
545 550 555 560

Leu Asp Arg Glu Gln Leu Arg Val Lys Met Asp Arg Glu Leu Glu Gln
565 570 575

Leu Thr Thr Thr Tyr Ser Lys Glu Lys Met Arg Val Arg Cys Ser Gln
580 585 590

Asn Asn Glu Leu Asp Lys Arg Lys Lys Asp Ile Glu Asp Gly Glu Lys
595 600 605

Lys Met Lys Lys Thr Lys Asn Ser Gln Asn Gln Gln Gln Met Lys Leu
610 615 620

Tyr Ser Ala Gln Gln Leu Lys Glu Tyr Lys Tyr Asn Lys Glu Ala Gln
625 630 635 640

Lys Thr Arg Leu Arg Ser Leu Asn Met Pro Arg Ser Thr Tyr Glu Asn
645 650 655

Ala Met Lys Glu Val Lys Ala Asp Leu Asn Arg Val Lys Asp Ala Arg
660 665 670

Glu Asn Asp Phe Asp Glu Lys Leu Arg Ala Glu Leu Glu Asp Glu Ile
675 680 685

Val Arg Tyr Arg Arg Gln Gln Leu Ser Asn Leu His Gln Leu Glu Glu
690 695 700

Gln Leu Asp Asp Glu Asp Val Asn Val Gln Glu Arg Gln Met Asp Thr
705 710 715 720

Arg His Gly Leu Leu Ser Lys Gln His Glu Met Thr Arg Asp Leu Glu
725 730 735

Ile Gln His Leu Asn Glu Leu His Ala Met Lys Lys Arg His Leu Glu
740 745 750

Thr Gln His Glu Ala Glu Ser Ala Ser Gln Asn Glu Tyr Thr Gln Arg
755 760 765

Gln Gln Asp Glu Leu Arg Lys Lys His Ala Met Gln Ser Arg Gln Gln
770 775 780

Pro Arg Asp Leu Lys Ile Gln Glu Ala Gln Ile Arg Lys Gln Tyr Arg
785 790 795 800

Gln Val Val Lys Thr Gln Thr Arg Gln Phe Lys Leu Tyr Leu Thr Gln
805 810 815

Met Val Gln Val Val Pro Lys Asp Glu Gln Lys Glu Leu Thr Ser Arg
820 825 830

Leu Lys Gln Asp Gln Met Gln Lys Val Ala Leu Leu Ala Ser Gln Tyr
835 840 845

Glu Ser Gln Ile Lys Lys Met Val Gln Asp Lys Thr Val Lys Leu Glu
850 855 860

Ser Trp Gln Glu Asp Glu Gln Arg Val Leu Ser Glu Lys Leu Glu Lys
865 870 875 880

Glu Leu Glu Glu Leu Ile Ala Tyr Gln Lys Lys Thr Arg Ala Thr Leu
885 890 895

Glu Glu Gln Ile Lys Lys Glu Arg Thr Ala Leu Glu Glu Arg Ile Gly
900 905 910

Thr Arg Arg Ala Met Leu Glu Gln Lys Ile Ile Glu Glu Arg Glu Gln
915 920 925

Met Gly Glu Met Arg Arg Leu Lys Lys Glu Gln Ile Arg Asp Arg His
930 935 940

Ser Gln Glu Arg His Arg Leu Glu Asn His Phe Val Arg Thr Gly Ser
945 950 955 960

Thr Ser Arg Ser Ser Gly Gly Ile Ala Pro Gly Val Gly Asn Ser Ser
965 970 975

Ser Ile Gln Met Ala Met
980

<210> 91
<211> 842
<212> PRT
<213> KHS1_h

<400> 91

Leu Arg Pro Ala Ala Asp Ile Leu Arg Arg Asn Pro Gln Gln Asp Tyr
1 5 10 15

Glu Leu Val Gln Arg Val Gly Ser Gly Thr Tyr Gly Asp Val Tyr Lys
20 25 30

Ala Arg Asn Val His Thr Gly Glu Leu Ala Ala Val Lys Ile Ile Lys
35 40 45

Leu Glu Pro Gly Asp Asp Phe Ser Leu Ile Gln Gln Glu Ile Phe Met
50 55 60

Val Lys Glu Cys Lys His Cys Asn Ile Val Ala Tyr Phe Gly Ser Tyr
65 70 75 80

Leu Ser Arg Glu Lys Leu Trp Ile Cys Met Glu Tyr Cys Gly Gly Gly
85 90 95

Ser Leu Gln Asp Ile Tyr His Val Thr Gly Pro Leu Ser Glu Leu Gln
100 105 110

Ile Ala Tyr Val Cys Arg Glu Thr Leu Gln Gly Leu Ala Tyr Leu His
115 120 125

Thr Lys Gly Lys Met His Arg Asp Ile Lys Gly Ala Asn Ile Leu Leu
130 135 140

Thr Asp His Gly Asp Val Lys Leu Ala Asp Phe Gly Val Ala Ala Lys
145 150 155 160

Ile Thr Ala Thr Ile Ala Lys Arg Lys Ser Phe Ile Gly Thr Pro Tyr
165 170 175

Trp Met Ala Pro Glu Val Ala Ala Val Glu Lys Asn Gly Gly Tyr Asn
180 185 190

Gln Leu Cys Asp Ile Trp Ala Val Gly Ile Thr Ala Ile Glu Leu Gly
195 200 205

Glu Leu Gln Pro Pro Met Phe Asp Leu His Pro Met Arg Ala Leu Phe
210 215 220

Leu Met Ser Lys Ser Asn Phe Gln Pro Pro Lys Leu Lys Asp Lys Thr
225 230 235 240

Lys Trp Ser Ser Thr Phe His Asn Phe Val Lys Ile Ala Leu Thr Lys
245 250 255

Asn Pro Lys Lys Arg Pro Thr Ala Glu Arg Leu Leu Thr His Thr Phe
260 265 270

Val Ala Gln Pro Gly Leu Ser Arg Ala Leu Ala Val Glu Leu Leu Asp
275 280 285

Lys Val Asn Asn Pro Asp Asn His Ala His Tyr Thr Glu Ala Asp Asp
290 295 300

Asp Asp Phe Glu Pro His Ala Ile Ile Arg His Thr Ile Arg Ser Thr
305 310 315 320

Asn Arg Asn Ala Arg Ala Glu Arg Thr Ala Ser Glu Ile Asn Phe Asp
325 330 335

Lys Leu Gln Phe Glu Pro Pro Leu Arg Lys Glu Thr Glu Ala Arg Asp
340 345 350

Glu Met Gly Leu Ser Ser Asp Pro Asn Phe Met Leu Gln Trp Asn Pro
355 360 365

Phe Val Asp Gly Ala Asn Thr Gly Lys Ser Thr Ser Lys Arg Ala Ile
370 375 380

Pro Pro Pro Leu Pro Pro Lys Pro Arg Ile Ser Ser Tyr Pro Glu Asp
385 390 395 400

Asn Phe Pro Asp Glu Glu Lys Ala Ser Thr Ile Lys His Cys Pro Asp
405 410 415

Ser Glu Ser Arg Ala Pro Gln Ile Leu Arg Arg Gln Ser Ser Pro Ser
420 425 430

Cys Gly Pro Val Ala Glu Thr Ser Ser Ile Gly Asn Gly Asp Gly Ile
435 440 445

Ser Lys Leu Met Ser Glu Asn Thr Glu Gly Ser Ala Gln Ala Pro Gln
450 455 460

Leu Pro Arg Lys Asn Asp Lys Arg Asp Phe Pro Lys Pro Ala Ile Asn
465 470 475 480

Gly Leu Pro Pro Thr Pro Lys Val Leu Met Gly Ala Cys Phe Ser Lys
485 490 495

Val Phe Asp Gly Cys Pro Leu Lys Ile Asn Cys Ala Thr Ser Trp Ile
500 505 510

His Pro Asp Thr Lys Asp Gln Tyr Ile Ile Phe Gly Thr Glu Asp Gly
515 520 525

Ile Tyr Thr Leu Asn Leu Asn Glu Leu His Glu Ala Thr Met Glu Gln
530 535 540

Leu Phe Pro Arg Lys Cys Thr Trp Leu Tyr Val Ile Asn Asn Thr Leu
545 550 555 560

Met Ser Leu Ser Glu Gly Lys Thr Phe Gln Leu Tyr Ser His Asn Leu
565 570 575

Ile Ala Leu Phe Glu His Ala Lys Lys Pro Gly Leu Ala Ala His Ile
580 585 590

Gln Thr His Arg Phe Pro Asp Arg Ile Leu Pro Arg Lys Phe Ala Leu
595 600 605

Thr Thr Lys Ile Pro Asp Thr Lys Gly Cys His Lys Cys Cys Ile Val
610 615 620

Arg Asn Pro Tyr Thr Gly His Lys Tyr Leu Cys Gly Ala Leu Gln Ser
625 630 635 640

Gly Ile Val Leu Leu Gln Trp Tyr Glu Pro Met Gln Lys Phe Met Leu
645 650 655

Ile Lys His Phe Asp Phe Pro Leu Pro Ser Pro Leu Asn Val Phe Glu
660 665 670

Met Leu Val Ile Pro Glu Gln Glu Tyr Pro Met Val Cys Val Ala Ile
675 680 685

Ser Lys Gly Thr Glu Ser Asn Gln Val Val Gln Phe Glu Thr Ile Asn
690 695 700

Leu Asn Ser Ala Ser Ser Trp Phe Thr Glu Ile Gly Ala Gly Ser Gln
705 710 715 720

Gln Leu Asp Ser Ile His Val Thr Gln Leu Glu Arg Asp Thr Val Leu
725 730 735

Val Cys Leu Asp Lys Phe Val Lys Ile Val Asn Leu Gln Gly Lys Leu
740 745 750

Lys Ser Ser Lys Lys Leu Ala Ser Glu Leu Ser Phe Asp Phe Arg Ile
755 760 765

Glu Ser Val Val Cys Leu Gln Asp Ser Val Leu Ala Phe Trp Lys His
770 775 780

Gly Met Gln Gly Lys Ser Phe Lys Ser Asp Glu Val Thr Gln Glu Ile
785 790 795 800

Ser Asp Glu Thr Arg Val Phe Arg Leu Leu Gly Ser Asp Arg Val Val
805 810 815

Val Leu Glu Ser Arg Pro Thr Glu Asn Pro Thr Ala His Ser Asn Leu
820 825 830

Tyr Ile Leu Ala Gly His Glu Asn Ser Tyr

835 840

<210> 92
<211> 911
<212> PRT
<213> LOK_m

<400> 92

Met Ala Phe Ala Asn Phe Arg Arg Ile Leu Arg Leu Ser Thr Phe Glu
1 5 10 15

Lys Arg Lys Ser Arg Glu Tyr Glu His Val Arg Arg Asp Leu Asp Pro
20 25 30

Asn Asp Val Trp Glu Ile Val Gly Glu Leu Gly Asp Gly Ala Phe Gly
35 40 45

Lys Val Tyr Lys Ala Lys Asn Lys Glu Thr Gly Ala Leu Ala Ala Ala
50 55 60

Lys Val Ile Glu Thr Lys Ser Glu Glu Glu Leu Glu Asp Tyr Ile Val
65 70 75 80

Glu Ile Glu Ile Leu Ala Thr Cys Asp His Pro Tyr Ile Val Lys Leu
85 90 95

Leu Gly Ala Tyr Tyr Tyr Asp Gly Lys Leu Trp Ile Met Ile Glu Phe
100 105 110

Cys Pro Gly Gly Ala Val Asp Ala Ile Met Leu Glu Leu Asp Arg Gly
115 120 125

Leu Thr Glu Pro Gln Ile Gln Val Val Cys Arg Gln Met Leu Glu Ala
130 135 140

Leu Asn Phe Leu His Gly Lys Arg Ile Ile His Arg Asp Leu Lys Ala
145 150 155 160

Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg Leu Ala Asp Phe
165 170 175

Gly Val Ser Ala Lys Asn Leu Lys Thr Leu Gln Lys Arg Asp Ser Phe
180 185 190

Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Leu Cys Glu Thr
195 200 205

Met Lys Asp Ala Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly
210 215 220

Ile Thr Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu
225 230 235 240

Asn Pro Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr
245 250 255

Leu Leu Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys
260 265 270

Ile Ala Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu
275 280 285

Leu Gln His Pro Phe Val Ser Arg Val Thr Ser Asn Lys Ala Leu Arg
290 295 300

Glu Leu Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp
305 310 315 320

Gly Arg Glu Asp Gly Glu Glu Glu Asp Ala Val Asp Ala Val Pro Pro
325 330 335

Leu Val Asn His Thr Gln Asp Ser Ala Asn Val Thr Gln Pro Ser Leu
340 345 350

Asp Ser Asn Lys Leu Leu Gln Asp Ser Ser Thr Pro Leu Pro Pro Ser
355 360 365

Gln Pro Gln Glu Pro Val Asn Gly Pro Cys Ser Gln Pro Ser Gly Asp
370 375 380

Gly Pro Leu Gln Thr Thr Ser Pro Ala Asp Gly Leu Ser Lys Asn Asp
385 390 395 400

Asn Asp Leu Lys Val Pro Val Pro Leu Arg Lys Ser Arg Pro Leu Ser
405 410 415

Met Asp Ala Arg Ile Gln Met Asp Glu Glu Lys Gln Ile Pro Asp Gln
420 425 430

Asp Glu Asn Pro Ser Pro Ala Ala Ser Lys Ser Gln Lys Ala Asn Gln
435 440 445

Ser Arg Pro Asn Ser Ser Ala Leu Glu Thr Leu Gly Gly Glu Ala Leu
450 455 460

Thr Asn Gly Gly Leu Glu Leu Pro Ser Ser Val Thr Pro Ser His Ser
465 470 475 480

Lys Arg Ala Ser Asp Cys Ser Asn Leu Ser Thr Ser Glu Ser Met Asp
485 490 495

Tyr Gly Thr Ser Leu Ser Ala Asp Leu Ser Leu Asn Lys Glu Thr Gly
500 505 510

Ser Leu Ser Leu Lys Gly Ser Lys Leu His Asn Lys Thr Leu Lys Arg
515 520 525

Thr Arg Arg Phe Val Val Asp Gly Val Glu Val Ser Ile Thr Thr Ser
530 535 540

Lys Ile Ile Ser Glu Asp Glu Lys Lys Asp Glu Glu Met Arg Phe Leu
545 550 555 560

Arg Arg Gln Glu Leu Arg Glu Leu Arg Leu Leu Gln Lys Glu Glu His
565 570 575

Arg Asn Gln Thr Gln Leu Ser Ser Lys His Glu Leu Gln Leu Glu Gln
580 585 590

Met His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe Tyr
595 600 605

Asp Val Glu Leu Glu Asn Leu Glu Arg Gln Gln Lys Gln Gln Val Glu
610 615 620

Lys Met Glu Gln Asp His Ser Val Arg Arg Lys Glu Glu Ala Lys Arg
625 630 635 640

Ile Arg Leu Glu Gln Asp Arg Asp Tyr Ala Lys Phe Gln Glu Gln Leu
645 650 655

Lys Gln Met Lys Lys Glu Val Lys Ser Glu Val Glu Lys Leu Pro Arg
660 665 670

Gln Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Ser Gln
675 680 685

Lys Lys Gln Arg Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu Asp
690 695 700

Leu Glu Leu Ala Met Arg Lys Leu Thr Thr Glu Asn Arg Arg Glu Ile
705 710 715 720

Cys Asp Lys Glu Arg Asp Cys Leu Ser Lys Lys Gln Glu Leu Leu Arg
725 730 735

Asp Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln Glu
740 745 750

Arg His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu Gln
755 760 765

Arg His Asp Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met Gln
770 775 780

Arg Tyr Asn Gln Arg Met Met Glu Gln Leu Lys Val Arg Gln Gln Gln
785 790 795 800

Glu Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Asp Gly Glu Thr Arg
805 810 815

Met Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Ala Gly Ser Ala

820 825 830

Ser Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu Lys
835 840 845

Arg Gln Lys Ala Glu Arg Leu Gln Gln Gln Gln Lys His Glu His Gln
850 855 860

Met Arg Asp Met Val Ala Gln Cys Glu Ser Asn Met Ser Glu Leu Gln
865 870 875 880

Gln Leu Gln Asn Glu Lys Cys Tyr Leu Leu Val Glu His Glu Thr Gln
885 890 895

Lys Leu Lys Ala Leu Asp Glu Ser His Asn Gln Ser Leu Lys Glu
900 905 910

<210> 93
<211> 545
<212> PRT
<213> PAK1_h

<400> 93

Met Ser Asn Asn Gly Leu Asp Ile Gln Asp Lys Pro Pro Ala Pro Pro
1 5 10 15

Met Arg Asn Thr Ser Thr Met Ile Gly Ala Gly Ser Lys Asp Ala Gly
20 25 30

Thr Leu Asn His Gly Ser Lys Pro Leu Pro Pro Asn Pro Glu Glu Lys
35 40 45

Lys Lys Lys Asp Arg Phe Tyr Arg Ser Ile Leu Pro Gly Asp Lys Thr
50 55 60

Asn Lys Lys Lys Glu Lys Glu Arg Pro Glu Ile Ser Leu Pro Ser Asp
65 70 75 80

Phe Glu His Thr Ile His Val Gly Phe Asp Ala Val Thr Gly Glu Phe
85 90 95

Thr Gly Met Pro Glu Gln Trp Ala Arg Leu Leu Gln Thr Ser Asn Ile
100 105 110

Thr Lys Ser Glu Gln Lys Lys Asn Pro Gln Ala Val Leu Asp Val Leu
115 120 125

Glu Phe Tyr Asn Ser Lys Lys Thr Ser Asn Ser Gln Lys Tyr Met Ser
130 135 140

Phe Thr Asp Lys Ser Ala Glu Asp Tyr Asn Ser Ser Asn Ala Leu Asn
145 150 155 160

Val Lys Ala Val Ser Glu Thr Pro Ala Val Pro Pro Val Ser Glu Asp
165 170 175

Glu Asp Asp Asp Asp Asp Asp Ala Thr Pro Pro Pro Val Ile Ala Pro
180 185 190

Arg Pro Glu His Thr Lys Ser Val Tyr Thr Arg Ser Val Ile Glu Pro
195 200 205

Leu Pro Val Thr Pro Thr Arg Asp Val Ala Thr Ser Pro Ile Ser Pro
210 215 220

Thr Glu Asn Asn Thr Thr Pro Pro Asp Ala Leu Thr Leu Asn Thr Glu
225 230 235 240

Lys Gln Lys Lys Lys Pro Lys Met Ser Asp Glu Glu Ile Leu Glu Lys
245 250 255

Leu Arg Ser Ile Val Ser Val Gly Asp Pro Lys Lys Lys Tyr Thr Arg
260 265 270

Phe Glu Lys Ile Gly Gln Gly Ala Ser Gly Thr Val Tyr Thr Ala Met
275 280 285

Asp Val Ala Thr Gly Gln Glu Val Ala Ile Lys Gln Met Asn Leu Gln
290 295 300

Gln Gln Pro Lys Lys Glu Leu Ile Ile Asn Glu Ile Leu Val Met Arg
305 310 315 320

Glu Asn Lys Asn Pro Asn Ile Val Asn Tyr Leu Asp Ser Tyr Leu Val
325 330 335

Gly Asp Glu Leu Trp Val Val Met Glu Tyr Leu Ala Gly Gly Ser Leu
340 345 350

Thr Asp Val Val Thr Glu Thr Cys Met Asp Glu Gly Gln Ile Ala Ala
355 360 365

Val Cys Arg Glu Cys Leu Gln Ala Leu Glu Ser Leu His Ser Asn Gln
370 375 380

Val Ile His Arg Asp Ile Lys Ser Asp Asn Ile Leu Leu Gly Met Asp
385 390 395 400

Gly Ser Val Lys Leu Thr Asp Phe Gly Phe Cys Ala Gln Ile Thr Pro
405 410 415

Glu Gln Ser Lys Arg Ser Thr Met Val Gly Thr Pro Tyr Trp Met Ala
420 425 430

Pro Glu Val Val Thr Arg Lys Ala Tyr Gly Pro Lys Val Asp Ile Trp
435 440 445

Ser Leu Gly Ile Met Ala Ile Glu Met Ile Glu Gly Glu Pro Pro Tyr
450 455 460

Leu Asn Glu Asn Pro Leu Arg Ala Leu Tyr Leu Ile Ala Thr Asn Gly
465 470 475 480

Thr Pro Glu Leu Gln Asn Pro Glu Lys Leu Ser Ala Ile Phe Arg Asp
485 490 495

Phe Leu Asn Arg Cys Leu Glu Met Asp Val Glu Lys Arg Gly Ser Ala
500 505 510

Lys Glu Leu Leu Gln His Gln Phe Leu Lys Ile Ala Lys Pro Leu Ser
515 520 525

Ser Leu Thr Pro Leu Ile Ala Ala Ala Lys Glu Ala Thr Lys Asn Asn
530 535 540

His
545

<210> 94
<211> 506
<212> PRT
<213> PAK65_h

<400> 94

Met Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Ser Ala Asn
1 5 10 15

His Ser Leu Lys Pro Leu Pro Ser Val Pro Glu Glu Lys Lys Pro Arg
20 25 30

His Lys Ile Ile Ser Ile Phe Ser Gly Thr Glu Lys Gly Ser Lys Lys
35 40 45

Lys Glu Lys Glu Arg Pro Glu Ile Ser Pro Pro Ser Asp Phe Glu His
50 55 60

Thr Ile His Val Gly Phe Asp Thr Val Thr Gly Glu Phe Thr Gly Met
65 70 75 80

Pro Glu Gln Trp Ala Arg Leu Leu Gln Thr Ser Asn Ile Thr Lys Leu
85 90 95

Glu Gln Lys Lys Asn Pro Gln Ala Val Leu Asp Val Leu Lys Phe Tyr
100 105 110

Asp Ser Asn Thr Val Lys Gln Lys Tyr Leu Ser Phe Thr Pro Pro Glu
115 120 125

```
Lys Asp Gly Phe Pro Ser Gly Thr Pro Ala Leu Asn Ala Lys Gly Thr
    130                 135                 140

Glu Ala Pro Ala Val Val Thr Glu Glu Glu Asp Asp Asp Glu Glu Thr
145                 150                 155                 160

Ala Pro Pro Val Ile Ala Pro Arg Pro Asp His Thr Lys Ser Ile Tyr
                165                 170                 175

Thr Arg Ser Val Ile Asp Pro Val Pro Ala Pro Val Gly Asp Ser His
            180                 185                 190

Val Asp Gly Ala Ala Lys Ser Leu Asp Lys Gln Lys Lys Lys Thr Lys
        195                 200                 205

Met Thr Asp Glu Glu Ile Met Glu Lys Leu Arg Thr Ile Val Ser Ile
    210                 215                 220

Gly Asp Pro Lys Lys Lys Tyr Thr Arg Tyr Glu Lys Ile Gly Gln Gly
225                 230                 235                 240

Ala Ser Gly Thr Val Phe Thr Ala Thr Asp Val Ala Leu Gly Gln Glu
                245                 250                 255

Val Ala Ile Lys Gln Ile Asn Leu Gln Lys Gln Pro Lys Lys Glu Leu
            260                 265                 270

Ile Ile Asn Glu Ile Leu Val Met Lys Glu Leu Lys Asn Pro Asn Ile
        275                 280                 285

Val Asn Phe Leu Asp Ser Tyr Leu Val Gly Asp Glu Leu Phe Val Val
    290                 295                 300

Met Glu Tyr Leu Ala Gly Arg Ser Leu Thr Asp Val Val Thr Glu Thr
305                 310                 315                 320

Cys Met Asp Glu Ala Gln Ile Ala Ala Val Cys Arg Glu Cys Leu Gln
                325                 330                 335

Ala Leu Glu Phe Leu His Ala Asn Gln Val Ile His Arg Asp Ile Lys
            340                 345                 350

Ser Asp Asn Val Leu Leu Gly Met Glu Gly Ser Val Lys Leu Thr Asp
        355                 360                 365

Phe Gly Phe Cys Ala Gln Ile Thr Pro Glu Gln Ser Lys Arg Ser Thr
    370                 375                 380

Met Val Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Thr Arg Lys
385                 390                 395                 400

Ala Tyr Gly Pro Lys Val Asp Ile Trp Ser Leu Gly Ile Met Ala Ile
                405                 410                 415

Glu Met Val Glu Gly Glu Pro Pro Tyr Leu Asn Glu Asn Pro Leu Arg
```

420 425 430

Ala Leu Tyr Leu Ile Ala Thr Asn Gly Thr Pro Glu Leu Gln Asn Pro
435 440 445

Glu Lys Leu Ser Pro Ile Phe Arg Asp Phe Leu Asn Arg Cys Leu Glu
450 455 460

Met Asp Val Glu Lys Arg Gly Ser Ala Lys Glu Leu Leu Gln His Pro
465 470 475 480

Phe Leu Lys Leu Ala Lys Pro Leu Ser Ser Leu Thr Pro Leu Ile Met
485 490 495

Ala Ala Lys Glu Ala Met Lys Ser Asn Arg
500 505

<210> 95
<211> 544
<212> PRT
<213> PAK3_m

<400> 95

Met Ser Asp Ser Leu Asp Asn Glu Glu Lys Pro Pro Ala Pro Pro Leu
1 5 10 15

Arg Met Asn Ser Asn Asn Arg Asp Ser Ser Ala Leu Asn His Ser Ser
20 25 30

Lys Pro Leu Pro Met Ala Pro Glu Glu Lys Asn Lys Lys Ala Arg Leu
35 40 45

Arg Ser Ile Phe Pro Gly Gly Gly Asp Lys Thr Asn Lys Lys Lys Glu
50 55 60

Lys Glu Arg Pro Glu Ile Ser Leu Pro Ser Asp Phe Glu His Thr Ile
65 70 75 80

His Val Gly Phe Asp Ala Val Thr Gly Glu Phe Thr Gly Ile Pro Glu
85 90 95

Gln Trp Ala Arg Leu Leu Gln Thr Ser Asn Ile Thr Lys Leu Glu Gln
100 105 110

Lys Lys Asn Pro Gln Ala Val Leu Asp Val Leu Lys Phe Tyr Asp Ser
115 120 125

Lys Glu Thr Val Asn Asn Gln Lys Tyr Met Ser Phe Thr Ser Gly Asp
130 135 140

Lys Ser Ala His Gly Tyr Ile Ala Ala His Gln Ser Asn Thr Lys Thr
145 150 155 160

Gly Ser Glu Pro Pro Leu Ala Pro Pro Val Ser Glu Glu Glu Asp Glu
165 170 175

Glu Glu Glu Glu Glu Glu Asp Asp Asn Glu Pro Pro Pro Val Ile Ala
180 185 190

Pro Arg Pro Glu His Thr Lys Ser Ile Tyr Thr Arg Ser Val Val Glu
195 200 205

Ser Ile Ala Ser Pro Ala Ala Pro Asn Lys Glu Asp Ile Pro Pro Ser
210 215 220

Ala Glu Asn Ala Asn Ser Thr Thr Leu Tyr Arg Asn Thr Asp Arg Gln
225 230 235 240

Arg Lys Lys Ser Lys Met Thr Asp Glu Glu Ile Leu Glu Lys Leu Arg
245 250 255

Ser Ile Val Ser Val Gly Asp Pro Lys Lys Lys Tyr Thr Arg Leu Glu
260 265 270

Lys Ile Gly Gln Gly Ala Ser Gly Thr Val Tyr Thr Ala Leu Asp Ile
275 280 285

Ala Thr Gly Gln Glu Val Ala Ile Lys Gln Met Asn Leu Gln Gln Gln
290 295 300

Pro Lys Lys Glu Leu Ile Ile Asn Glu Ile Leu Val Met Arg Glu Asn
305 310 315 320

Lys Asn Pro Asn Ile Val Asn Tyr Leu Asp Ser Tyr Leu Val Gly Asp
325 330 335

Glu Leu Trp Val Val Met Glu Tyr Leu Ala Gly Gly Ser Leu Thr Asp
340 345 350

Val Val Thr Glu Thr Cys Met Asp Val Gly Gln Ile Ala Ala Val Cys
355 360 365

Arg Glu Cys Leu Gln Ala Leu Asp Phe Leu His Ser Asn Gln Val Ile
370 375 380

His Arg Asp Ile Lys Ser Asp Asn Ile Leu Leu Gly Met Asp Gly Ser
385 390 395 400

Val Lys Leu Thr Asp Phe Gly Phe Cys Ala Gln Ile Thr Pro Glu Gln
405 410 415

Ser Lys Arg Ser Thr Met Val Gly Thr Pro Tyr Trp Met Ala Pro Glu
420 425 430

Val Val Thr Arg Lys Ala Tyr Gly Pro Lys Val Asp Ile Trp Ser Leu
435 440 445

Gly Ile Met Ala Ile Glu Met Val Glu Gly Glu Pro Pro Tyr Leu Asn

450 455 460

Glu Asn Pro Leu Arg Ala Leu Tyr Leu Ile Ala Thr Asn Gly Thr Pro
465 470 475 480

Glu Leu Gln Asn Pro Glu Arg Leu Ser Ala Val Phe His Asp Phe Leu
485 490 495

Asn Arg Cys Leu Glu Met Asp Val Asp Arg Arg Gly Ser Ala Lys Glu
500 505 510

Leu Leu Gln His Pro Phe Leu Lys Leu Ala Lys Pro Leu Ser Ser Leu
515 520 525

Thr Pro Leu Ile Ile Ala Ala Lys Glu Ala Ile Lys Asn Ser Ser Arg
530 535 540

<400> 96
<210> 96
<211> 2110
<212> DNA
<213> Full Length Mammalian (Human) STLK5

<400> 96

```
ggccaagacg gtcggggctg cttgctaact ccaggaacag gtttaagttt ttgaaactga      60
agtaggtcta cacagtagga actcatgtca tttcttgtaa gtaaaccaga gcgaatcagg     120
cggtgggtct cggaaaagtt cattgttgag ggcttaagag atttggaact atttggagac     180
caatgatgcg agctcagagt caatagcatc cttctctaaa caggaggtca tgagtagctt     240
tctgccagag ggagggtgtt acgagctgct cactgtgata ggcaaaggat ttgaggacct     300
gatgactgtg aatctagcaa ggtacaaacc aacaggagag tacgtgactg tacggaggat     360
taacctagaa gcttgttcca atgagatggt aacattcttg cagggcgagc tgcatgtctc     420
caaactcttc aaccatccca atatcgtgcc atatcgagcc acttttattg cagacaatga     480
gctgtgggtt gtcacatcat tcatggcata cggttctgca aaagatctca tctgtacaca     540
cttcatggat ggcatgaatg agctggcgat tgcttacatc ctgcaggggg tgctgaaggc     600
cctcgactac atccaccaca tgggatatgt acacaggagt gtcaaagcca gccacatcct     660
gatctctgtg gatgggaagg tctacctgtc tggtttgcgc agcaacctca gcatgataag     720
ccatgggcag cggcagcgag tggtccacga ttttcccaag tacagtgtca aggttctgcc     780
gtggctcagc cccgaggtcc tccagcagaa tctccagggt tatgatgcca agtctgacat     840
ctacagtgtg ggaatcacag cctgtgaact ggccaacggc catgtcccct ttaaggatat     900
gcctgccacc cagatgctgc tagagaaact gaacggcaca gtgccctgcc tgttggatac     960
cagcaccatc cccgctgagg agctgaccat gagcccttcg cgctcagtgg ccaactctgg    1020
cctgagtgac agcctgacca ccagcacccc ccggccctcc aacggtgact cgccctccca    1080
cccctaccac cgaaccttct ccccccactt ccaccacttt gtggagcagt gccttcagcg    1140
caacccggat gccaggccca gtgccagcac cctcctgaac cactctttct tcaagcagat    1200
caagcgacgt gcctcagagg ctttgcccga attgcttcgt cctgtcaccc ccatcaccaa    1260
ttttgagggc agccagtctc aggaccacag tggaatcttt ggcctggtaa caaacctgga    1320
agagctggag gtggacgatt gggagttctg agcctctgca aactgtgcgc attctccagc    1380
cagggatgca gaggccaccc agaggccctt cctgagggcc ggccacattc ccgccctcct    1440
gggcagattg ggtagaaagg acattcttcc aggaaagttg actgctgact gattgggaaa    1500
gaaaatcctg gagagatact tcactgctcc aaggcttttg agacacaagg gaatctcaac    1560
aaccagggat caggagggtc caaagccgac attcccagtc ctgtgagctc aggtgacctc    1620
```

```
ctccgcagaa gagagatgct gctctggccc tgggagctga attccaagcc cagggtttgg    1680
ctccttaaac ccgaggaccg ccacctcttc ccagtgcttg cgaccagcct cattctattt    1740
aactttgctc tcagatgcct cagatgctat aggtcagtga aagggcaagt agtaagctgc    1800
ctgcctccct tccctcagac ctctccctca taattccaga gaagggcatt tctgtctttt    1860
taagcacaga ctaaggctgg aacagtccat ccttatccct cttctggctt gggccctgac    1920
acctaagtct ttcccacggt ttatgtgtgt gcctcattcc tttcccacca agaatccatc    1980
ttagcgcctc ctgccagctg ccctggtgct ttctccaagg gccatcagtg tcttgcctag    2040
cttgagggct taagtcctta tgctgtgtta gtttcgttgt cagaacaaat taaaattttc    2100
agagacgctg                                                           2110
```

<210> 97
<211> 373
<212> PRT
<213> Full Length Mammalian (Human) STLK 5

<400> 97

```
Met Ser Ser Phe Leu Pro Glu Gly Gly Cys Tyr Glu Leu Leu Thr Val
1               5                   10                  15

Ile Gly Lys Gly Phe Glu Asp Leu Met Thr Val Asn Leu Ala Arg Tyr
            20                  25                  30

Lys Pro Thr Gly Glu Tyr Val Thr Val Arg Arg Ile Asn Leu Glu Ala
        35                  40                  45

Cys Ser Asn Glu Met Val Thr Phe Leu Gln Gly Glu Leu His Val Ser
    50                  55                  60

Lys Leu Phe Asn His Pro Asn Ile Val Pro Tyr Arg Ala Thr Phe Ile
65                  70                  75                  80

Ala Asp Asn Glu Leu Trp Val Val Thr Ser Phe Met Ala Tyr Gly Ser
                85                  90                  95

Ala Lys Asp Leu Ile Cys Thr His Phe Met Asp Gly Met Asn Glu Leu
            100                 105                 110

Ala Ile Ala Tyr Ile Leu Gln Gly Val Leu Lys Ala Leu Asp Tyr Ile
        115                 120                 125

His His Met Gly Tyr Val His Arg Ser Val Lys Ala Ser His Ile Leu
    130                 135                 140

Ile Ser Val Asp Gly Lys Val Tyr Leu Ser Gly Leu Arg Ser Asn Leu
145                 150                 155                 160

Ser Met Ile Ser His Gly Gln Arg Gln Arg Val Val His Asp Phe Pro
                165                 170                 175

Lys Tyr Ser Val Lys Val Leu Pro Trp Leu Ser Pro Glu Val Leu Gln
            180                 185                 190
```

```
Gln Asn Leu Gln Gly Tyr Asp Ala Lys Ser Asp Ile Tyr Ser Val Gly
        195                 200                 205

Ile Thr Ala Cys Glu Leu Ala Asn Gly His Val Pro Phe Lys Asp Met
    210                 215                 220

Pro Ala Thr Gln Met Leu Leu Glu Lys Leu Asn Gly Thr Val Pro Cys
225                 230                 235                 240

Leu Leu Asp Thr Ser Thr Ile Pro Ala Glu Glu Leu Thr Met Ser Pro
                245                 250                 255

Ser Arg Ser Val Ala Asn Ser Gly Leu Ser Asp Ser Leu Thr Thr Ser
            260                 265                 270

Thr Pro Arg Pro Ser Asn Gly Asp Ser Pro Ser His Pro Tyr His Arg
        275                 280                 285

Thr Phe Ser Pro His Phe His His Phe Val Glu Gln Cys Leu Gln Arg
    290                 295                 300

Asn Pro Asp Ala Arg Pro Ser Ala Ser Thr Leu Leu Asn His Ser Phe
305                 310                 315                 320

Phe Lys Gln Ile Lys Arg Arg Ala Ser Glu Ala Leu Pro Glu Leu Leu
                325                 330                 335

Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser Gln Asp
            340                 345                 350

His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Leu Glu Val
        355                 360                 365

Asp Asp Trp Glu Phe
    370
```

<210> 98
<211> 2001
<212> DNA
<213> Mammalian (Human) STLK6

<400> 98

```
aaggaagata aaacaaaagc cttctttgga atagatggat ttttgtcact ttctgtgtga
actaaagtga ttcaatgtct cttttggatt gcttctgcac ttcaagaaca caagttgaat      120
cactcagacc tgaaaaacag tctgaaacca gtatccatca atacttggtt gatgagccaa
ccctttcctg gtcacgtcca tccactagag ccagtgaagt actatgttcc accaacgttt      240
ctcactatga gctccaagta gaaataggaa gaggatttga caacttgact tctgtccatc      300
ttgcacggca tactcccacg ggaacactgg taactataaa aattacaaat ctggaaaact      360
gcaatgaaga acgcctgaaa gctttacaga aagccgtgat tctatcccac tttttccggc      420
```

```
atcccaatat tacaacttat tggacagttt tcactgttgg cagctggctt tgggttattt      480
ctccatttat ggcctatggt tcagcaagtc aactcttgag gacctatttt cctgaaggaa      540
tgagtgaaac tttaataaga aacattctct ttggagccgt gagagggttg aactatctgc      600
accaaaatgg ctgtattcac aggagtatta aagccagcca tatcctcatt tctggtgatg      660
gcctagtgac cctctctggc ctttcccatc tgcatagttt ggttaagcat ggacagaggc      720
atagggctgt gtatgatttc ccacagttca gcacatcagt gcagccgtgg ctgagtccag      780
aactactgag acaggattta catgggtata atgtgaagtc agatatttac agtgttggga      840
ttacagcatg tgaattagcc agtgggcagg tgcctttcca ggacatgcat agaactcaga      900
tgctgttaca gaaactgaaa ggtcctcctt atagcccatt ggatatcagt attttccctc      960
aatcagaatc cagaatgaaa aattcccagt caggtgtaga ctctgggatt ggagaaagtg     1020
tgcttgtctc cagtggaact cacacagtaa atagtgaccg attacacaca ccatcctcaa     1080
aaactttctc tcctgccttc tttagcttgg tacagctctg tttgcaacaa gatcctgaga     1140
aaaggccatc agcaagcagt ttattgtccc atgttttctt caaacagatg aaagaagaaa     1200
gccaggattc aatactttca ctgttgcctc ctgcttataa caagccatca atatcattgc     1260
ctccagtgtt accttggact gagccagaat gtgattttcc tgatgaaaaa gactcatact     1320
gggaattcta gggctgccaa atcattttat gtcctatata cttgacactt tctccttgct     1380
gctttttctt ctgtatttct aggtacaaat accagaatta tacttgaaaa tacagttggt     1440
gcactggaga atctattatt taaaaccact ctgttcaaag gggcaccagt ttgtagtccc     1500
tctgtttcgc acagagtact atgacaagga aacatcagaa ttactaatct agctagtgtc     1560
atttattctg gaattttttt ctaagctgtg actaactctt tttatctctc aatataattt     1620
ttgagccagt taattttttt cagtattttg ctgtcccttg ggaatgggcc ctcagaggac     1680
agtgcttcca agtacatctt ctcccagatt ctctggcctt tttaatgagc tattgttaaa     1740
ccaacaggct agtttatctt acatcagacc cttttctggt agagggaaaa tgtttgtgct     1800
ttcccttttt cttctgttaa tacttatggt aacacctaac tgagcctcac tcacattaaa     1860
tgattcactt gaaatatata cagaaattgt aatttgcttt tttttaaaaa agggggctaa     1920
agtaacactt tcctacttat gtaaattata gatcctaaat tcacgcaccc cgtgggagct     1980
caataaagat ttactgaatt g                                               2001
```

<210> 99
<211> 373
<212> PRT
<213> Mammalian (Human) STLK6

<400> 99

```
Met Ser Ser Phe Leu Pro Glu Gly Gly Cys Tyr Glu Leu Leu Thr Val
1               5                   10                  15

Ile Gly Lys Gly Phe Glu Asp Leu Met Thr Val Asn Leu Ala Arg Tyr
            20                  25                  30

Lys Pro Thr Gly Glu Tyr Val Thr Val Arg Arg Ile Asn Leu Glu Ala
        35                  40                  45

Cys Ser Asn Glu Met Val Thr Phe Leu Gln Gly Glu Leu His Val Ser
    50                  55                  60

Lys Leu Phe Asn His Pro Asn Ile Val Pro Tyr Arg Ala Thr Phe Ile
65                  70                  75                  80

Ala Asp Asn Glu Leu Trp Val Val Thr Ser Phe Met Ala Tyr Gly Ser
                85                  90                  95
```

Ala Lys Asp Leu Ile Cys Thr His Phe Met Asp Gly Met Asn Glu Leu
100 105 110

Ala Ile Ala Tyr Ile Leu Gln Gly Val Leu Lys Ala Leu Asp Tyr Ile
115 120 125

His His Met Gly Tyr Val His Arg Ser Val Lys Ala Ser His Ile Leu
130 135 140

Ile Ser Val Asp Gly Lys Val Tyr Leu Ser Gly Leu Arg Ser Asn Leu
145 150 155 160

Ser Met Ile Ser His Gly Gln Arg Gln Arg Val Val His Asp Phe Pro
165 170 175

Lys Tyr Ser Val Lys Val Leu Pro Trp Leu Ser Pro Glu Val Leu Gln
180 185 190

Gln Asn Leu Gln Gly Tyr Asp Ala Lys Ser Asp Ile Tyr Ser Val
195 200 205

Ile Thr Ala Cys Glu Leu Ala Asn Gly His Val Pro Phe Lys Asp Met
210 215 220

Pro Ala Thr Gln Met Leu Leu Glu Lys Leu Asn Gly Thr Val Pro
225 230 235 240

Leu Leu Asp Thr Ser Thr Ile Pro Ala Glu Glu Leu Thr Met Ser Pro
245 250 255

Ser Arg Ser Val Ala Asn Ser Gly Leu Ser Asp Ser Leu Thr Thr
260 265 270

Thr Pro Arg Pro Ser Asn Gly Asp Ser Pro Ser His Pro Tyr His Arg
275 280 285

Thr Phe Ser Pro His Phe His His Phe Val Glu Gln Cys Leu Gln
290 295 300

Asn Pro Asp Ala Arg Pro Ser Ala Ser Thr Leu Leu Asn His Ser Phe
305 310 315 320

Phe Lys Gln Ile Lys Arg Arg Ala Ser Glu Ala Leu Pro Glu Leu
325 330 335

Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser Gln Asp
340 345 350

His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Leu Glu
355 360 365

Asp Asp Trp Glu Phe

370

<210> 100
<211> 311
<212> DNA
<213> Mammalian (Human) STLK7

<400> 100

tcaacaggga cgattacgag ctgcaggagg tgatcgggag tggagcaact gctgtagtcc
aagcagctta ttgtgcccct aaaaaggaga aagtggcaat caaacggata aaccttgaga
aatgtcaaac tagcatggat gaactcctga aagaaattca agccatgagt caatgccatc 180
atcctaatat tgtatcttac tacacatctt ttgtggtaaa agatgagctg tggcttgtca 240
tgaagctgct aagtggaggt tctgttctgg atattattaa gcacattgtg gcaaaagggg 300
aacacaaaag t 311

<210> 101
<211> 103
<212> PRT
<213> Mammalian (Human) STLK7

<400> 101

Asn Arg Asp Asp Tyr Glu Leu Gln Glu Val Ile Gly Ser Gly Ala Thr
1 5 10 15

Ala Val Val Gln Ala Ala Tyr Cys Ala Pro Lys Lys Glu Lys Val Ala
20 25 30

Ile Lys Arg Ile Asn Leu Glu Lys Cys Gln Thr Ser Met Asp Glu Leu
35 40 45

Leu Lys Glu Ile Gln Ala Met Ser Gln Cys His His Pro Asn Ile Val
50 55 60

Ser Tyr Tyr Thr Ser Phe Val Val Lys Asp Glu Leu Trp Leu Val Met
65 70 75 80

Lys Leu Leu Ser Gly Gly Ser Val Leu Asp Ile Ile Lys His Ile Val
85 90 95

Ala Lys Gly Glu His Lys Ser
100

<210> 102
<211> 2806

<212> DNA
<213> Full Length Mammalian (Human) PAK5

<400> 102

```
cgggagtgtc cgcggtggtg gcggtgcaag agagctgaag gaggcgcgag ggcgcggagt      60
tccaggccga gcagttaggc cgcgagcgac tgcggcgccg agccgatgag taacccgaag     120
cccctagagg agtggtcacc tgcctgaggg cacttctgtc ccaccagcat cagaccaggc     180
cgcaccgagt ccccggcacc atgtttggga agaggaagaa gcgggtggag atctccgcgc     240
cgtccaactt cgagcaccgc gtgcacacgg gcttcgacca gcacgagcag aagttcacgg     300
ggctgccccg ccagtggcag agcctgatcg aggagtcggc tcgccggccc aagcccctcg     360
tcgaccccgc ctgcatcacc tccatccagc ccggggcccc caagaccatc gtgcggggca     420
gcaaaggtgc caaagatggg gccctcacgc tgctgctgga cgagtttgag aacatgtcgg     480
tgacacgctc caactccctg cggagagaca gcccgccgcc gcccgcccgt gcccgccagg     540
aaaatgggat gccagaggag ccggccacca cggccagagg gggcccaggg aaggcaggca     600
gccgaggccg gttcgccggt cacagcgagg cgggtggcgg cagtggtgac aggcgacggg     660
cggggccaga gaagaggccc aagtcttcca gggagggctc aggggtccc caggagtcct     720
cccgggacaa acgcccccctc tccgggcctg atgtcggcac cccccagcct gctggtctgg     780
ccagtggggc gaaactggca gctggccggc cctttaacac ctacccgagg gctgacacgg     840
accacccatc ccggggtgcc caggggggagc ctcatgacgt ggcccctaac gggccatcag     900
cggggggcct ggccatcccc cagtcctcct cctcctcctc ccggcctccc acccgagccc     960
gaggtgcccc cagccctgga gtgctgggac cccacgcctc agagccccag ctggcccctc    1020
cagcctgcac ccccgccgcc cctgctgttc ctgggccccc tggcccccgc tcaccacagc    1080
gggagccaca gcgagtatcc catgagcagt tccgggctgc cctgcagctg gtggtggacc    1140
caggcgaccc ccgctcctac ctggacaact tcatcaagat tggcgagggc tccacgggca    1200
tcgtgtgcat cgccaccgtg cgcagctcgg gcaagctggt ggccgtcaag aagatggacc    1260
tgcgcaagca gcagaggcgc gagctgctct tcaacgaggt ggtaatcatg agggactacc    1320
agcacgagaa tgtggtggag atgtacaaca gctacctggt gggggacgag ctctgggtgg    1380
tcatggagtt cctggaagga ggcgccctca ccgacatcgt cacccacacc aggatgaacg    1440
aggagcagat cgcggccgtg tgccttgcag tgctgcaggc cctgtcggtg ctccacgccc    1500
agggcgtcat ccaccgggac atcaagagcg actcgatcct gctgacccat gatggcaggg    1560
tgaagctgtc agactttggg ttctgcgccc aggtgagcaa ggaagtgccc cgaaggaagt    1620
cgctggtcgg cacgccctac tggatggccc cagagctcat ctcccgcctt ccctacgggc    1680
cagaggtaga catctggtcg ctggggataa tggtgattga gatggtggac ggagagcccc    1740
cctacttcaa cgagccaccc ctcaaagcca tgaagatgat tcgggacaac ctgccacccc    1800
gactgaagaa cctgcacaag gtgtcgccat ccctgaaggg cttcctggac cgcctgctgg    1860
tgcgagaccc tgcccagcgg gccacggcag ccgagctgct gaagcaccca ttcctggcca    1920
aggcagggcc gcctgccagc atcgtgcccc tcatgcgcca gaaccgcacc agatgaggcc    1980
cagcgccctt cccctcaacc aaagagcccc cccgggtcac ccccgcccca ctgaggccag    2040
tagggggcca ggcctcccac tcctcccagc ccgggagatg ctccgcgtgg caccaccctc    2100
cttgctgggg gtagatgaga ccctactact gaactccagt tttgatctcg tgacttttag    2160
aaaaacacag ggactcgtgg gagcaagcga ggctcccagg acccccaccc tctgggacag    2220
gccctccccc atgttcttct gtctccagga agggcagcgg ccctcccatc actggaagtc    2280
tgcagtgggg gtcgctgggg gtggagagaa cactaagagg tgaacatgta tgagtgtgtg    2340
cacgcgtgtg agtgtgcatg tgtgtgtgtg tgcaaaggtc cagccacccc gtcctccagc    2400
ccgcaagggg tgtctggcgc cttgcctgac acccagcccc ctctcccccct gagccattgt    2460
gggggtcgat catgaatgtc cgaagagtgg ccttttcccg tagccctgcg ccccctttct    2520
gtggctggat ggggagacag gtcagggccc cccaccctct ccagcccctg cagcaaatga    2580
ctactgcacc tggacagcct cctcttttct agaagtctat ttatattgtc attttataac    2640
actctagccc ctgcccttat tgggggacag atggtccctg tcctgcgggg tggccctggc    2700
agaaccactg cctgaagaac caggttcctg cccggtcagc gcagccccag cccgcccacc    2760
cctgcctcga gttagtttta caattaaaac attgtcttgt tttgtg                   2806
```

<210> 103
<211> 591
<212> PRT
<213> Full Length Mammalian (Human) PAK5hu

<400> 103

Met Phe Gly Lys Arg Lys Lys Arg Val Glu Ile Ser Ala Pro Ser Asn
1   5   10   15

Phe Glu His Arg Val His Thr Gly Phe Asp Gln His Glu Gln Lys Phe
            20   25   30

Thr Gly Leu Pro Arg Gln Trp Gln Ser Leu Ile Glu Glu Ser Ala Arg
        35   40   45

Arg Pro Lys Pro Leu Val Asp Pro Ala Cys Ile Thr Ser Ile Gln Pro
    50   55   60

Gly Ala Pro Lys Thr Ile Val Arg Gly Ser Lys Gly Ala Lys Asp Gly
65   70   75   80

Ala Leu Thr Leu Leu Leu Asp Glu Phe Glu Asn Met Ser Val Thr Arg
                85   90   95

Ser Asn Ser Leu Arg Arg Asp Ser Pro Pro Pro Pro Ala Arg Ala Arg
            100   105   110

Gln Glu Asn Gly Met Pro Glu Glu Pro Ala Thr Thr Ala Arg Gly Gly
        115   120   125

Pro Gly Lys Ala Gly Ser Arg Gly Arg Phe Ala Gly His Ser Glu Ala
    130   135   140

Gly Gly Gly Ser Gly Asp Arg Arg Arg Ala Gly Pro Glu Lys Arg Pro
145   150   155   160

Lys Ser Ser Arg Glu Gly Ser Gly Gly Pro Gln Glu Ser Ser Arg Asp
                165   170   175

Lys Arg Pro Leu Ser Gly Pro Asp Val Gly Thr Pro Gln Pro Ala Gly
            180   185   190

Leu Ala Ser Gly Ala Lys Leu Ala Ala Gly Arg Pro Phe Asn Thr Tyr
        195   200   205

Pro Arg Ala Asp Thr Asp His Pro Ser Arg Gly Ala Gln Gly Glu Pro
    210   215   220

His Asp Val Ala Pro Asn Gly Pro Ser Ala Gly Gly Leu Ala Ile Pro
225   230   235   240

Gln Ser Ser Ser Ser Ser Ser Arg Pro Pro Thr Arg Ala Arg Gly Ala
                245   250   255

```
Pro Ser Pro Gly Val Leu Gly Pro His Ala Ser Glu Pro Gln Leu Ala
            260                 265                 270

Pro Pro Ala Cys Thr Pro Ala Ala Pro Ala Val Pro Gly Pro Pro Gly
        275                 280                 285

Pro Arg Ser Pro Gln Arg Glu Pro Gln Arg Val Ser His Glu Gln Phe
    290                 295                 300

Arg Ala Ala Leu Gln Leu Val Val Asp Pro Gly Asp Pro Arg Ser Tyr
305                 310                 315                 320

Leu Asp Asn Phe Ile Lys Ile Gly Glu Gly Ser Thr Gly Ile Val Cys
                325                 330                 335

Ile Ala Thr Val Arg Ser Ser Gly Lys Leu Val Ala Val Lys Lys Met
            340                 345                 350

Asp Leu Arg Lys Gln Gln Arg Arg Glu Leu Leu Phe Asn Glu Val Val
        355                 360                 365

Ile Met Arg Asp Tyr Gln His Glu Asn Val Val Glu Met Tyr Asn Ser
    370                 375                 380

Tyr Leu Val Gly Asp Glu Leu Trp Val Val Met Glu Phe Leu Glu Gly
385                 390                 395                 400

Gly Ala Leu Thr Asp Ile Val Thr His Thr Arg Met Asn Glu Glu Gln
                405                 410                 415

Ile Ala Ala Val Cys Leu Ala Val Leu Gln Ala Leu Ser Val Leu His
            420                 425                 430

Ala Gln Gly Val Ile His Arg Asp Ile Lys Ser Asp Ser Ile Leu Leu
        435                 440                 445

Thr His Asp Gly Arg Val Lys Leu Ser Asp Phe Gly Phe Cys Ala Gln
    450                 455                 460

Val Ser Lys Glu Val Pro Arg Arg Lys Ser Leu Val Gly Thr Pro Tyr
465                 470                 475                 480

Trp Met Ala Pro Glu Leu Ile Ser Arg Leu Pro Tyr Gly Pro Glu Val
                485                 490                 495

Asp Ile Trp Ser Leu Gly Ile Met Val Ile Glu Met Val Asp Gly Glu
            500                 505                 510

Pro Pro Tyr Phe Asn Glu Pro Pro Leu Lys Ala Met Lys Met Ile Arg
        515                 520                 525

Asp Asn Leu Pro Pro Arg Leu Lys Asn Leu His Lys Val Ser Pro Ser
    530                 535                 540
```

Leu Lys Gly Phe Leu Asp Arg Leu Leu Val Arg Asp Pro Ala Gln Arg
545 550 555 560

Ala Thr Ala Ala Glu Leu Leu Lys His Pro Phe Leu Ala Lys Ala Gly
565 570 575

Pro Pro Ala Ser Ile Val Pro Leu Met Arg Gln Asn Arg Thr Arg
580 585 590

<210> 104
<211> 3684
<212> DNA
<213> Full Length Mammalian (Human) ZC4

<400> 104

```
atggcgggac ctgggggctg gagggacagg gaggtcacgg atctgggcca cctgccggat      60
ccaactggaa tattctcact agataaaacc attggccttg gtacttatgg cagaatctat     120
ttgggacttc atgagaagac tggtgcattt acagctgtta aagtgatgaa cgctcgtaag     180
gatgaggaag aggatctcag gactgaactc aaccttctga ggaagtactc tttccacaaa     240
aacattgtgt ccttctatgg agcatttttc aagctgagtc cccctggtca gcggcaccaa     300
ctttggatgg tgatggagtt atgtgcagca ggttcggtca ctgatgtagt gagaatgacc     360
agtaatcaga gtttaaaaga agattggatt gcttatatct gccgagaaat ccttcagggc     420
ttagctcacc ttcacgcaca ccgagtaatt caccgggaca tcaaaggtca gaatgtgctg     480
ctgactcata atgctgaagt aaaactggtt gattttggag tgagtgccca ggtgagcaga     540
actaatggaa gaaggaatag tttcattggg acaccatact ggatggcacc tgaggtgatt     600
gactgtgatg aggacccaag acgctcctat gattacagaa gtgatgtgtg gtctgtggga     660
attactgcca ttgaaatggc tgaaggagcc cctcctctgt gtaaccttca acccttggaa     720
gctctcttcg ttattttgcg ggaatctgct cccacagtca aatccagcgg atggtcccgt     780
aagttccaca atttcatgga aaagtgtacg ataaaaaatt tcctgtttcg tcctacttct     840
gcaaacatgc ttcaacaccc atttgttcgg gatataaaaa atgaacgaca tgttgttgag     900
tcattaacaa ggcatcttac tggaatcatt aaaaaaagac agaaaaaaga acaggcacgg     960
gagaaaaaat caaaagtttc tactctgagg caagcactgg caaaaagact atcaccaaag    1020
aggttcaggg caaagtcatc atggagacct gaaaagcttg aactctcgga tttagaagcc    1080
cgcaggcaaa ggcgccaacg cagatgggaa gatatcttta atcagcatga ggaagaattg    1140
agacaagttg ataaagacaa agaagatgaa tcatcagaca atgatgaagt atttcattcg    1200
attcaggctg aagtccagat agagccattg aagccataca tttcaaatcc taaaaaaatt    1260
gaggttcaag agagatctcc ttctgtgcct aacaaccagg atcatgcaca tcatgtcaag    1320
ttctcttcaa gcgttcctca gcggtctctt ttggaacaag ctcagaagcc cattgacatc    1380
agacaaagga gttcgcaaaa tcgtcaaaat tggctggcag catcaggtga ttcaaagcac    1440
aaaattttag caggcaaaac acagagctac tgtttaacaa tttatatttc agaagtcaag    1500
aaagaagaat ttcaagaagg aatgaatcaa aagtgtcagg gagcccaagt aggattagga    1560
cctgaaggcc attgtatttg gcaattgggt gaatcttctt ctgaggaaga aagtcctgtg    1620
actggaagga ggtctcagtc atcaccacct tattctacta ttgatcagaa gttgctggtt    1680
gacatccatg ttccagatgg atttaaagta ggaaaaatat caccccctgt atacttgaca    1740
aacgaatggg taggctataa tgcactctct gaaatcttcc ggaatgattg gttaactccg    1800
gcacctgtca ttcagccacc tgaagaggat ggtgattatg ttgaactcta tgatgccagt    1860
gctgatactg atggtgatga tgatgatgag tctaatgata cttttgaaga tacctatgat    1920
catgccaatg gcaatgatga cttggataac caggttgatc aggctaatga tgtttgtaaa    1980
gaccatgatg atgacaacaa taagtttgtt gatgatgtaa ataataatta ttatgaggcg    2040
cctagttgtc caagggcaag ctatggcaga gatggaagct gcaagcaaga tggttatgat    2100
ggaagtcgtg gaaaagagga agcctacaga ggctatggaa gccatacagc caatagaagc    2160
catggaggaa gtgcagccag tgaggacaat gcagccattg gagatcagga agaacatgca    2220
gccaatatag gcagtgaaag aagaggcagt gagggtgatg gaggtaaggg agtcgttcga    2280
```

```
accagtgaag agagtggagc ccttggactc aatggagaag aaaattgctc agagacagat    2340
ggtccaggat tgaagagacc tgcgtctcag gactttgaat atctacagga ggagccaggt    2400
ggtggaaatg aggcctcaaa tgccattgac tcaggtgctg caccgtcagc acctgatcat    2460
gagagtgaca ataaggacat atcagaatca tcaacacaat cagatttttc tgccaatcac    2520
tcatctcctt ccaaaggttc tgggatgtct gctgatgcta actttgccag tgccatctta    2580
tacgctggat tcgtagaagt acctgaggaa tcacctaagc aaccctctga agtcaatgtt    2640
aacccactct atgtctctcc tgcatgtaaa aaaccactaa tccacatgta tgaaaaggag    2700
ttcacttctg agatctgctg tggttctttg tggggagtca atttgctgtt gggaacccga    2760
tctaatctat atctgatgga cagaagtgga aaggctgaca ttactaaact tataaggcga    2820
agaccattcc gccagattca agtcttagag ccactcaatt tgctgattac catctcaggt    2880
cataagaaca gacttcgggt gtatcatctg acctggttga ggaacaagat tttgaataat    2940
gatccagaaa gtaaaagaag gcaagaagaa atgctgaaga cagaggaagc ctgcaaagct    3000
attgataagt taacaggctg tgaacacttc agtgtcctcc aacatgaaga aacaacatat    3060
attgcaattg ctttgaaatc atcaattcac ctttatgcat gggcaccaaa gtcctttgat    3120
gaaagcactg ctattaaagt atttccaaca cttgatcata agccagtgac agttgacctg    3180
gctattggtt ctgaaaaaag actaaagatt ttcttcagct cagcagatgg atatcacctc    3240
atcgatgcag aatctgaggt tatgtctgat gtgaccctgc caaagaatcc cctggaaatc    3300
attataccac agaatatcat cattttacct gattgcttgg gaattggcat gatgctcacc    3360
ttcaatgctg aagccctctc tgtggaagca aatgaacaac tcttcaagaa gatccttgaa    3420
atgtggaaag acataccatc ttctatagct tttgaatgta cacagcgaac cacaggatgg    3480
ggccaaaagg ccattgaagt gcgctctttg caatccaggg ttctggaaag tgagctgaag    3540
cgcaggtcaa ttaagaagct gagattcctg tgcacccggg gtgacaagct gttctttacc    3600
tctaccctgc gcaatcacca cagccgggtt tacttcatga cacttggaaa acttgaagag    3660
ctccaaagca attatgatgt ctaa                                           3684
```

<210> 105
<211> 1227
<212> PRT
<213> Full Length Mammalian (Human) ZC4

<400> 105

```
Met Ala Gly Pro Gly Gly Trp Arg Asp Arg Glu Val Thr Asp Leu Gly
1               5                   10                  15

His Leu Pro Asp Pro Thr Gly Ile Phe Ser Leu Asp Lys Thr Ile Gly
            20                  25                  30

Leu Gly Thr Tyr Gly Arg Ile Tyr Leu Gly Leu His Glu Lys Thr Gly
        35                  40                  45

Ala Phe Thr Ala Val Lys Val Met Asn Ala Arg Lys Asp Glu Glu Glu
    50                  55                  60

Asp Leu Arg Thr Glu Leu Asn Leu Leu Arg Lys Tyr Ser Phe His Lys
65                  70                  75                  80

Asn Ile Val Ser Phe Tyr Gly Ala Phe Phe Lys Leu Ser Pro Pro Gly
                85                  90                  95

Gln Arg His Gln Leu Trp Met Val Met Glu Leu Cys Ala Ala Gly Ser
            100                 105                 110
```

Val Thr Asp Val Val Arg Met Thr Ser Asn Gln Ser Leu Lys Glu Asp
115 120 125

Trp Ile Ala Tyr Ile Cys Arg Glu Ile Leu Gln Gly Leu Ala His Leu
130 135 140

His Ala His Arg Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu
145 150 155 160

Leu Thr His Asn Ala Glu Val Lys Leu Val Asp Phe Gly Val Ser Ala
165 170 175

Gln Val Ser Arg Thr Asn Gly Arg Arg Asn Ser Phe Ile Gly Thr Pro
180 185 190

Tyr Trp Met Ala Pro Glu Val Ile Asp Cys Asp Glu Asp Pro Arg Arg
195 200 205

Ser Tyr Asp Tyr Arg Ser Asp Val Trp Ser Val Gly Ile Thr Ala Ile
210 215 220

Glu Met Ala Glu Gly Ala Pro Pro Leu Cys Asn Leu Gln Pro Leu Glu
225 230 235 240

Ala Leu Phe Val Ile Leu Arg Glu Ser Ala Pro Thr Val Lys Ser Ser
245 250 255

Gly Trp Ser Arg Lys Phe His Asn Phe Met Glu Lys Cys Thr Ile Lys
260 265 270

Asn Phe Leu Phe Arg Pro Thr Ser Ala Asn Met Leu Gln His Pro Phe
275 280 285

Val Arg Asp Ile Lys Asn Glu Arg His Val Val Glu Ser Leu Thr Arg
290 295 300

His Leu Thr Gly Ile Ile Lys Lys Arg Gln Lys Lys Glu Gln Ala Arg
305 310 315 320

Glu Lys Lys Ser Lys Val Ser Thr Leu Arg Gln Ala Leu Ala Lys Arg
325 330 335

Leu Ser Pro Lys Arg Phe Arg Ala Lys Ser Ser Trp Arg Pro Glu Lys
340 345 350

Leu Glu Leu Ser Asp Leu Glu Ala Arg Arg Gln Arg Arg Gln Arg Arg
355 360 365

Trp Glu Asp Ile Phe Asn Gln His Glu Glu Glu Leu Arg Gln Val Asp
370 375 380

Lys Asp Lys Glu Asp Glu Ser Ser Asp Asn Asp Glu Val Phe His Ser
385 390 395 400

Ile Gln Ala Glu Val Gln Ile Glu Pro Leu Lys Pro Tyr Ile Ser Asn
405 410 415

Pro Lys Lys Ile Glu Val Gln Glu Arg Ser Pro Ser Val Pro Asn Asn
420 425 430

Gln Asp His Ala His His Val Lys Phe Ser Ser Ser Val Pro Gln Arg
435 440 445

Ser Leu Leu Glu Gln Ala Gln Lys Pro Ile Asp Ile Arg Gln Arg Ser
450 455 460

Ser Gln Asn Arg Gln Asn Trp Leu Ala Ala Ser Gly Asp Ser Lys His
465 470 475 480

Lys Ile Leu Ala Gly Lys Thr Gln Ser Tyr Cys Leu Thr Ile Tyr Ile
485 490 495

Ser Glu Val Lys Lys Glu Glu Phe Gln Glu Gly Met Asn Gln Lys Cys
500 505 510

Gln Gly Ala Gln Val Gly Leu Gly Pro Glu Gly His Cys Ile Trp Gln
515 520 525

Leu Gly Glu Ser Ser Ser Glu Glu Glu Ser Pro Val Thr Gly Arg Arg
530 535 540

Ser Gln Ser Ser Pro Pro Tyr Ser Thr Ile Asp Gln Lys Leu Leu Val
545 550 555 560

Asp Ile His Val Pro Asp Gly Phe Lys Val Gly Lys Ile Ser Pro Pro
565 570 575

Val Tyr Leu Thr Asn Glu Trp Val Gly Tyr Asn Ala Leu Ser Glu Ile
580 585 590

Phe Arg Asn Asp Trp Leu Thr Pro Ala Pro Val Ile Gln Pro Pro Glu
595 600 605

Glu Asp Gly Asp Tyr Val Glu Leu Tyr Asp Ala Ser Ala Asp Thr Asp
610 615 620

Gly Asp Asp Asp Asp Glu Ser Asn Asp Thr Phe Glu Asp Thr Tyr Asp
625 630 635 640

His Ala Asn Gly Asn Asp Asp Leu Asp Asn Gln Val Asp Gln Ala Asn
645 650 655

Asp Val Cys Lys Asp His Asp Asp Asp Asn Asn Lys Phe Val Asp Asp
660 665 670

Val Asn Asn Asn Tyr Tyr Glu Ala Pro Ser Cys Pro Arg Ala Ser Tyr
675 680 685

Gly Arg Asp Gly Ser Cys Lys Gln Asp Gly Tyr Asp Gly Ser Arg Gly
690 695 700

Lys Glu Glu Ala Tyr Arg Gly Tyr Gly Ser His Thr Ala Asn Arg Ser
705 710 715 720

His Gly Gly Ser Ala Ala Ser Glu Asp Asn Ala Ala Ile Gly Asp Gln
725 730 735

Glu Glu His Ala Ala Asn Ile Gly Ser Glu Arg Arg Gly Ser Glu Gly
740 745 750

Asp Gly Gly Lys Gly Val Val Arg Thr Ser Glu Glu Ser Gly Ala Leu
755 760 765

Gly Leu Asn Gly Glu Glu Asn Cys Ser Glu Thr Asp Gly Pro Gly Leu
770 775 780

Lys Arg Pro Ala Ser Gln Asp Phe Glu Tyr Leu Gln Glu Glu Pro Gly
785 790 795 800

Gly Gly Asn Glu Ala Ser Asn Ala Ile Asp Ser Gly Ala Ala Pro Ser
805 810 815

Ala Pro Asp His Glu Ser Asp Asn Lys Asp Ile Ser Glu Ser Ser Thr
820 825 830

Gln Ser Asp Phe Ser Ala Asn His Ser Ser Pro Ser Lys Gly Ser Gly
835 840 845

Met Ser Ala Asp Ala Asn Phe Ala Ser Ala Ile Leu Tyr Ala Gly Phe
850 855 860

Val Glu Val Pro Glu Glu Ser Pro Lys Gln Pro Ser Glu Val Asn Val
865 870 875 880

Asn Pro Leu Tyr Val Ser Pro Ala Cys Lys Lys Pro Leu Ile His Met
885 890 895

Tyr Glu Lys Glu Phe Thr Ser Glu Ile Cys Cys Gly Ser Leu Trp Gly
900 905 910

Val Asn Leu Leu Leu Gly Thr Arg Ser Asn Leu Tyr Leu Met Asp Arg
915 920 925

Ser Gly Lys Ala Asp Ile Thr Lys Leu Ile Arg Arg Arg Pro Phe Arg
930 935 940

Gln Ile Gln Val Leu Glu Pro Leu Asn Leu Leu Ile Thr Ile Ser Gly
945 950 955 960

His Lys Asn Arg Leu Arg Val Tyr His Leu Thr Trp Leu Arg Asn Lys
965 970 975

Ile Leu Asn Asn Asp Pro Glu Ser Lys Arg Arg Gln Glu Glu Met Leu
980 985 990

Lys Thr Glu Glu Ala Cys Lys Ala Ile Asp Lys Leu Thr Gly Cys Glu
995 1000 1005

His Phe Ser Val Leu Gln His Glu Glu Thr Thr Tyr Ile Ala Ile Ala
1010 1015 1020

Leu Lys Ser Ser Ile His Leu Tyr Ala Trp Ala Pro Lys Ser Phe Asp
1025 1030 1035 1040

Glu Ser Thr Ala Ile Lys Val Phe Pro Thr Leu Asp His Lys Pro Val
1045 1050 1055

Thr Val Asp Leu Ala Ile Gly Ser Glu Lys Arg Leu Lys Ile Phe Phe
1060 1065 1070

Ser Ser Ala Asp Gly Tyr His Leu Ile Asp Ala Glu Ser Glu Val Met
1075 1080 1085

Ser Asp Val Thr Leu Pro Lys Asn Pro Leu Glu Ile Ile Ile Pro Gln
1090 1095 1100

Asn Ile Ile Ile Leu Pro Asp Cys Leu Gly Ile Gly Met Met Leu Thr
1105 1110 1115 1120

Phe Asn Ala Glu Ala Leu Ser Val Glu Ala Asn Glu Gln Leu Phe Lys
1125 1130 1135

Lys Ile Leu Glu Met Trp Lys Asp Ile Pro Ser Ser Ile Ala Phe Glu
1140 1145 1150

Cys Thr Gln Arg Thr Thr Gly Trp Gly Gln Lys Ala Ile Glu Val Arg
1155 1160 1165

Ser Leu Gln Ser Arg Val Leu Glu Ser Glu Leu Lys Arg Arg Ser Ile
1170 1175 1180

Lys Lys Leu Arg Phe Leu Cys Thr Arg Gly Asp Lys Leu Phe Phe Thr
1185 1190 1195 1200

Ser Thr Leu Arg Asn His His Ser Arg Val Tyr Phe Met Thr Leu Gly
1205 1210 1215

Lys Leu Glu Glu Leu Gln Ser Asn Tyr Asp Val
1220 1225

<210> 106
<211> 2962
<212> DNA
<213> Full Length Mammalian (Human) GEK2

<400> 106

```
cgaagccaca gcccgagccc gagcccgagc ccgagccggc gccaccgcgc ccccggccat     60
ggcttttgcc aatttccgcc gcatcctgcg cctgtctacc ttcgagaaga gaaagtcccg    120
cgaatatgag cacgtccgcc gcgacctgga ccccaacgag gtgtgggaga tcgtgggcga    180
gctgggcgac ggcgccttcg gcaaggttta caaggccaag aataaggaga cgggtgcttt    240
ggctgcggcc aaagtcattg aaaccaagag tgaggaggag ctggaggact acatcgtgga    300
gattgagatc ctggccacct gcgaccaccc ctacattgtg aagctcctgg gagcctacta    360
tcacgacggg aagctgtgga tcatgattga gttctgtcca gggggagccg tggacgccat    420
catgctggag ctggacagag gcctcacgga gccccagata caggtggttt gccgccagat    480
gctagaagcc ctcaacttcc tgcacagcaa gaggatcatc caccgagatc tgaaagctgg    540
caacgtgctg atgaccctcg agggagacat caggctggct gactttggtg tgtctgccaa    600
gaatctgaag actctacaga aacgagattc cttcatcggc acgccttact ggatggcccc    660
cgaggtggtc atgtgtgaga ccatgaaaga cacgccctac gactacaaag ccgacatctg    720
gtccctgggc atcacgctga ttgagatggc ccagatcgag ccgccacacc acgagctcaa    780
ccccatgcgg gtcctgctaa agatcgccaa gtcggaccct cccacgctgc tcacgccctc    840
caagtggtct gtagagttcc gtgacttcct gaagatagcc ctggataaga acccagaaac    900
ccgacccagt gccgcgcagc tgctggagca tcccttcgtc agcagcatca ccagtaacaa    960
ggctctgcgg gagctggtgg ctgaggccaa ggccgaggtg atggaagaga tcgaagacgg   1020
ccgggatgag ggggaagagg aggacgccgt ggatgccgcc tccaccctgg agaaccatac   1080
tcagaactcc tctgaggtga gtccgccaag cctcaatgct gacaagcctc tcgaggagtc   1140
accttccacc ccgctggcac ccagccagtc tcaggacagt gtgaatgagc cctgcagcca   1200
gccctctggg gacagatccc tccaaaccac cagtccccca gtcgtggccc ctggaaatga   1260
gaacggcctg gcagtgcctg tgcccctgcg gaagtcccga cccgtgtcaa tggatgccag   1320
aattcaggta gcccaggaga agcaagttgc tgagcagggt ggggacctca gcccagcagc   1380
caacagatct caaaaggcca gccagagccg gcccaacagc agcgccctgg agaccttggg   1440
tggggagaag ctggccaatg gcagcctgga gccacctgcc caggcagctc cagggccttc   1500
caagagggac tcggactgca gcagcctctg cacctctgag agcatggact atggtaccaa   1560
tctctccact gacctgtcgc tgaacaaaga gatgggctct ctgtccatca aggacccgaa   1620
actgtacaaa aaaaccctca agcggacacg caaatttgtg gtggatggtg tggaggtgag   1680
catcaccacc tccaagatca tcagcgaaga tgagaagaag gatgaggaga tgagatttct   1740
caggcgccag gaactccgag agcttcggct gctccagaaa gaagagcatc ggaaccagac   1800
ccagctgagt aacaagcatg agctgcagct ggagcaaatg cataaacgtt ttgaacagga   1860
aatcaacgcc aagaagaagt tctttgacac ggaattagag aacctggagc gtcagcaaaa   1920
gcagcaagtg gagaagatgg agcaagacca tgccgtgcgc cgccgggagg aggccaggcg   1980
gatccgcctg gagcaggatc gggactacac caggttccaa gagcagctca aactgatgaa   2040
gaaagaggtg aagaacgagg tggagaagct cccccgacag cagcggaagg aaagcatgaa   2100
gcagaagatg gaggagcaca cgcagaaaaa gcagcttctt gaccgggact ttgtagccaa   2160
gcagaaggag gacctggagc tggccatgaa gaggctcacc accgacaaca ggcgggagat   2220
ctgtgacaag gagcgcgagt gcctcatgaa gaagcaggag ctccttcgag accgggaagc   2280
agccctgtgg gagatggaag agcaccagct gcaggagagg caccagctgg tgaagcagca   2340
gctcaaagac cagtacttcc tccagcggca cgagctgctg cgcaagcatg agaaggagcg   2400
ggagcagatg cagcgctaca accagcgcat gatagagcag ctgaaggtgc ggcagcaaca   2460
ggaaaaggcg cggctgccca agatccagag gagtgagggc aagacgcgca tggccatgta   2520
caagaagagc ctccacatca acggcggggg cagcgcagct gagcagcgtg agaagatcaa   2580
gcagttctcc cagcaggagg agaagaggca gaagtcggag cggctgcagc aacagcagaa   2640
acacgagaac cagatgcggg acatgctggc gcagtgcgag agcaacatga gcgagctgca   2700
gcagctgcag aatgaaaagt gccacctcct ggtagagcac gaaacccaga aactgaaggc   2760
cctggatgag agccataacc agaacctgaa ggaatggcgg gacaagcttc ggccgcgcaa   2820
gaaggctctg gaagaggatc tgaaccagaa gaagcgggag caggagatgt tcttcaagct   2880
gagcgaggag gcggagtgcc caaacccctc caccccaagc aaggccgcca agttcttccc   2940
ctacagctct ggggatgctt cc                                            2962
```

<210> 107
<211> 968
<212> PRT
<213> Full Length Mammalian (Human) GEK2

<400> 107

Met Ala Phe Ala Asn Phe Arg Arg Ile Leu Arg Leu Ser Thr Phe Glu
1   5   10   15

Lys Arg Lys Ser Arg Glu Tyr Glu His Val Arg Arg Asp Leu Asp Pro
            20   25   30

Asn Glu Val Trp Glu Ile Val Gly Glu Leu Gly Asp Gly Ala Phe Gly
        35   40   45

Lys Val Tyr Lys Ala Lys Asn Lys Glu Thr Gly Ala Leu Ala Ala Ala
    50   55   60

Lys Val Ile Glu Thr Lys Ser Glu Glu Glu Leu Glu Asp Tyr Ile Val
65   70   75   80

Glu Ile Glu Ile Leu Ala Thr Cys Asp His Pro Tyr Ile Val Lys Leu
                85   90   95

Leu Gly Ala Tyr Tyr His Asp Gly Lys Leu Trp Ile Met Ile Glu Phe
            100   105   110

Cys Pro Gly Gly Ala Val Asp Ala Ile Met Leu Glu Leu Asp Arg Gly
        115   120   125

Leu Thr Glu Pro Gln Ile Gln Val Val Cys Arg Gln Met Leu Glu Ala
    130   135   140

Leu Asn Phe Leu His Ser Lys Arg Ile Ile His Arg Asp Leu Lys Ala
145   150   155   160

Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg Leu Ala Asp Phe
                165   170   175

Gly Val Ser Ala Lys Asn Leu Lys Thr Leu Gln Lys Arg Asp Ser Phe
            180   185   190

Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Met Cys Glu Thr
        195   200   205

Met Lys Asp Thr Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly
    210   215   220

Ile Thr Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu
225   230   235   240

Asn Pro Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr
                245   250   255

Leu Leu Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys
260 265 270

Ile Ala Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu
275 280 285

Leu Glu His Pro Phe Val Ser Ser Ile Thr Ser Asn Lys Ala Leu Arg
290 295 300

Glu Leu Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp
305 310 315 320

Gly Arg Asp Glu Gly Glu Glu Glu Asp Ala Val Asp Ala Ala Ser Thr
325 330 335

Leu Glu Asn His Thr Gln Asn Ser Ser Glu Val Ser Pro Pro Ser Leu
340 345 350

Asn Ala Asp Lys Pro Leu Glu Glu Ser Pro Ser Thr Pro Leu Ala Pro
355 360 365

Ser Gln Ser Gln Asp Ser Val Asn Glu Pro Cys Ser Gln Pro Ser Gly
370 375 380

Asp Arg Ser Leu Gln Thr Thr Ser Pro Pro Val Val Ala Pro Gly Asn
385 390 395 400

Glu Asn Gly Leu Ala Val Pro Val Pro Leu Arg Lys Ser Arg Pro Val
405 410 415

Ser Met Asp Ala Arg Ile Gln Val Ala Gln Glu Lys Gln Val Ala Glu
420 425 430

Gln Gly Gly Asp Leu Ser Pro Ala Ala Asn Arg Ser Gln Lys Ala Ser
435 440 445

Gln Ser Arg Pro Asn Ser Ser Ala Leu Glu Thr Leu Gly Gly Glu Lys
450 455 460

Leu Ala Asn Gly Ser Leu Glu Pro Pro Ala Gln Ala Ala Pro Gly Pro
465 470 475 480

Ser Lys Arg Asp Ser Asp Cys Ser Ser Leu Cys Thr Ser Glu Ser Met
485 490 495

Asp Tyr Gly Thr Asn Leu Ser Thr Asp Leu Ser Leu Asn Lys Glu Met
500 505 510

Gly Ser Leu Ser Ile Lys Asp Pro Lys Leu Tyr Lys Lys Thr Leu Lys
515 520 525

Arg Thr Arg Lys Phe Val Val Asp Gly Val Glu Val Ser Ile Thr Thr
530 535 540

Ser Lys Ile Ile Ser Glu Asp Glu Lys Lys Asp Glu Glu Met Arg Phe
545 550 555 560

Leu Arg Arg Gln Glu Leu Arg Glu Leu Arg Leu Leu Gln Lys Glu Glu
565 570 575

His Arg Asn Gln Thr Gln Leu Ser Asn Lys His Glu Leu Gln Leu Glu
580 585 590

Gln Met His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe
595 600 605

Phe Asp Thr Glu Leu Glu Asn Leu Glu Arg Gln Gln Lys Gln Gln Val
610 615 620

Glu Lys Met Glu Gln Asp His Ala Val Arg Arg Arg Glu Glu Ala Arg
625 630 635 640

Arg Ile Arg Leu Glu Gln Asp Arg Asp Tyr Thr Arg Phe Gln Glu Gln
645 650 655

Leu Lys Leu Met Lys Lys Glu Val Lys Asn Glu Val Glu Lys Leu Pro
660 665 670

Arg Gln Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Thr
675 680 685

Gln Lys Lys Gln Leu Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu
690 695 700

Asp Leu Glu Leu Ala Met Lys Arg Leu Thr Thr Asp Asn Arg Arg Glu
705 710 715 720

Ile Cys Asp Lys Glu Arg Glu Cys Leu Met Lys Lys Gln Glu Leu Leu
725 730 735

Arg Asp Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln
740 745 750

Glu Arg His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu
755 760 765

Gln Arg His Glu Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met
770 775 780

Gln Arg Tyr Asn Gln Arg Met Ile Glu Gln Leu Lys Val Arg Gln Gln
785 790 795 800

Gln Glu Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Glu Gly Lys Thr
805 810 815

Arg Met Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Gly Gly Ser
820 825 830

Ala Ala Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu
835 840 845

Lys Arg Gln Lys Ser Glu Arg Leu Gln Gln Gln Gln Lys His Glu Asn
850 855 860

Gln Met Arg Asp Met Leu Ala Gln Cys Glu Ser Asn Met Ser Glu Leu
865 870 875 880

Gln Gln Leu Gln Asn Glu Lys Cys His Leu Leu Val Glu His Glu Thr
885 890 895

Gln Lys Leu Lys Ala Leu Asp Glu Ser His Asn Gln Asn Leu Lys Glu
900 905 910

Trp Arg Asp Lys Leu Arg Pro Arg Lys Lys Ala Leu Glu Glu Asp Leu
915 920 925

Asn Gln Lys Lys Arg Glu Gln Glu Met Phe Phe Lys Leu Ser Glu Glu
930 935 940

Ala Glu Cys Pro Asn Pro Ser Thr Pro Ser Lys Ala Ala Lys Phe Phe
945 950 955 960

Pro Tyr Ser Ser Gly Asp Ala Ser
965

<210> 108
<211> 11
<212> PRT
<213> Mammalian (human) ZC1 and/or ZC3
<220>
<223> "Xaa can stand for any amino acid

<400> 108

Leu Xaa Leu Xaa Leu Xaa Leu Xaa Leu Xaa Leu
1 5 10

<210> 109
<211> 20
<212> DNA
<213> Artificial Sequence
<220>
<223> Synthesized nucleic acid molecule

<400> 109

gcagcaagtg gagaagatgg 20

<210> 110

<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthesized nucleic acid molecule

<400> 110

ggaagcatcc ccagagctgt ag 22

<210> 111
<211> 12
<212> PRT
<213> Mammalian (Human) STLK2

<400> 111

Glu Lys Phe Gln Lys Cys Ser Ala Asp Glu Ser Pro
1 5 10

<210> 112
<211> 16
<212> PRT
<213> Mammalian (Human) STLK4

<400> 112

Ser Ile Ser Asn Ser Glu Leu Phe Pro Thr Thr Asp Pro Val Gly Thr
1 5 10 15

<210> 113
<211> 9
<212> PRT
<213> Mammalian (Human) SULU1

<400> 113

Leu Asp Phe Pro Lys Glu Asp Tyr Arg
1 5

<210> 114
<211> 12
<212> PRT
<213> Mammalian (Human) SULU1

<400> 114

His Gly Asp Pro Arg Pro Glu Pro Arg Pro Thr Gln
1 5 10

<210> 115
<211> 14
<212> PRT
<213> Mammalian (Human) SULU3

<400> 115

Pro Ser Thr Asn Arg Ala Gly Ser Leu Lys Asp Pro Glu Cys
1 5 10

<210> 116
<211> 19
<212> PRT
<213> Mammalian (Human) SULU3

<400> 116

Asp Pro Arg Thr Arg Ala Ser Asp Pro Gln Ser Pro Pro Gln Val Ser
1 5 10 15

Arg His Lys

<210> 117
<211> 16
<212> PRT
<213> Mammalian (Human) PAK4

<400> 117

Cys Leu Val Pro Leu Ile Gln Leu Tyr Arg Lys Gln Thr Ser Thr Cys
1 5 10 15

<210> 118
<211> 9
<212> PRT
<213> Mammalian (Human) PAK5

<400> 118

Pro Leu Met Arg Gln Asn Arg Thr Arg
1 5

<210> 119
<211> 16
<212> PRT
<213> Mammalian (Human) PAK5

<400> 119

Ser Gly Asp Arg Arg Arg Ala Gly Pro Glu Lys Arg Pro Lys Ser Ser
1 5 10 15

<210> 120
<211> 16
<212> PRT
<213> Mammalian (Human) PAK5

<400> 120

Cys Arg Arg Lys Ser Leu Val Gly Thr Pro Tyr Trp Met Ala Pro Glu
1 5 10 15

<210> 121
<211> 20
<212> PRT
<213> Mammalian (Human) ZC1

<400> 121

Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Pro Tyr Trp
1 5 10 15

Met Ala Pro Glu
20

<210> 122
<211> 15
<212> PRT
<213> Mammalian (Human) KHS1

<400> 122

Lys Arg Lys Ser Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu
1 5 10 15

<210> 123
<211> 15
<212> PRT
<213> Mammalian (Human) STLK2

<400> 123

Lys Arg Asn Thr Phe Val Gly Thr Pro Phe Trp Met Ala Pro Glu
1 5 10 15

<210> 124
<211> 15
<212> PRT
<213> Mammalian (Human) SULU1

<400> 124

Pro Ala Asn Ser Phe Val Gly Thr Pro Tyr Trp Met Ala Pro Glu
1 5 10 15

<210> 125
<211> 15
<212> PRT
<213> Mammalian (Human) ZC1

<400> 125

Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu
1 5 10 15

<210> 126
<211> 15
<212> PRT
<213> Mammalian (Human) ZC1

<400> 126

Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu
1 5 10 15

<210> 127
<211> 18
<212> PRT
<213> Mammalian (Human) STLK4

<400> 127

Arg Asn Lys Val Arg Lys Thr Phe Val Gly Thr Pro Cys Trp Met Ala
1   5   10   15

Pro Glu

<210> 128
<211> 22
<212> DNA
<213> Mammalian (Human) STLK3

<400> 128

ctcccatttc ctagcaaaat ca 22

<210> 129
<211> 22
<212> DNA
<213> Mammalian (Human) STLK3

<400> 129

agaggcagta ttgtcagatg ta 22

<210> 130
<211> 22
<212> DNA
<213> Mammalian (Human) STLK4

<400> 130

ccacacatgc gtatctctgt tg 22

<210> 131
<211> 24
<212> DNA
<213> Mammalian (Human) STLK4

<400>

ttgctagaat tcacatcagg taca 24

<210> 132
<211> 22
<212> DNA
<213> Mammalian (Human) ZC1

<400> 132

atccctggat cacactgctt ct 22

<210> 133
<211> 22
<212> DNA
<213> Mammalian (Human) ZC1

<400> 133

caaggtgttc tttgcctctg tt 22

<210> 134
<211> 21
<212> DNA
<213> Mammalian (Human) ZC2

<400> 134

agatggactg tactgggagg g 21

<210> 135
<211> 22
<212> DNA
<213> Mammalian (Human) ZC2

<400> 135

agaagagcac ttggcactta tc 22

<210> 136
<211> 20
<212> DNA
<213> Mammalian (Human) ZC3

<400> 136

catcatgaac tggtgacggg 20

<210> 137
<211> 23
<212> DNA
<213> Mammalian (Human) ZC3

<400> 137

ccagtgaaat caaaccagta aaa 23

<210> 138
<211> 24
<212> DNA
<213> Mammalian (Human) SULU1

<400> 138

caaaacctgg ccgtctcttc tatt 24

<210> 139
<211> 23
<212> DNA
<213> Mammalian (Human) SULU1

<400> 139

atttgtgcta ctgggattct gtg 23

<210> 140
<211> 24
<212> DNA
<213> Mammalian (Human) KHS2

<400> 140

gaatagcggt accatgatag aata 24

<210> 141

<211> 23
<212> DNA
<213> Mammalian (Human) KHS2

<400> 141

taccaaaaag agccaaaagt gtg 23

<210> 142
<211> 23
<212> DNA
<213> Mammalian (Human) PAK4

<400> 142

ctcagtattc tctccaaaga ttg 23

<210> 143
<211> 23
<212> DNA
<213> Mammalian (Human) PAK4

<400> 143

gatgttctct ccattctgta aag 23

<210> 144
<211> 21
<212> DNA
<213> Mammalian (Human) PAK5

<400> 144

catcactgga agtctgcagt g 21

<210> 145
<211> 20
<212> DNA
<213> Mammalian (Human) PAK5

<400> 145

caggtgcagt agtcatttgc 20

<210> 146
<211> 20
<212> DNA
<213> T7 phage

<400> 146

ggagctgtcg tattccagtc 20

<210> 147
<211> 21
<212> DNA
<213> T7 phage

<400> 147

aacccctcaa gacccgttta g 21